

Europäisches Patentamt

European Patent Office

Office européen des brevets



(11)

EP 1 078 917 A1

7

(12)

EUROPEAN PATENT APPLICATION

published in accordance with Art. 158(3) EPC

(43) Date of publication:
28.02.2001 Bulletin 2001/09

(21) Application number: 99902896.2

(22) Date of filing: 12.02.1999

(51) Int. Cl.⁷: **C07C 257/18**, A61K 31/27,
C07D 309/04, A61K 31/35,
A61K 31/41, C07D 257/04,
C07D 213/78, C07D 213/81,
A61K 31/44, C07D 317/68,
C07D 307/78, C07D 307/84,
C07D 307/22, C07D 307/68,
A61K 31/34, A61K 31/36,
C07D 239/36, A61K 31/505,
C07D 333/38, C07D 333/70,
A61K 31/38

(86) International application number:
PCT/JP99/00622

(87) International publication number:
WO 99/41231 (19.08.1999 Gazette 1999/33)

(84) Designated Contracting States:
AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU
MC NL PT SE

(30) Priority: 17.02.1998 JP 7681598

(71) Applicant:
ONO PHARMACEUTICAL CO., LTD.
Osaka-shi, Osaka 541-8526 (JP)

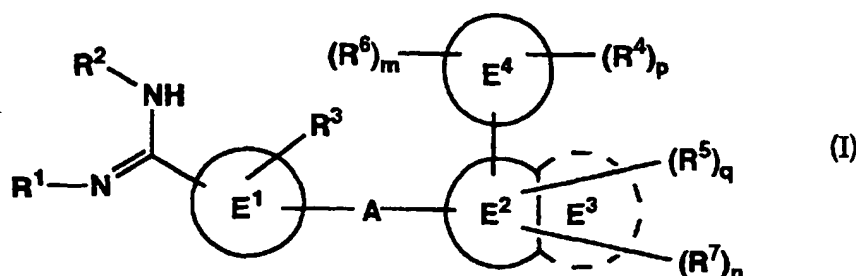
(72) Inventors:
• SENOKUCHI, Kazuhiko,
Ono Pharmaceutical Co., Ltd.
Mishima-gun, Osaka 618-8585 (JP)

• OGAWA, Koji,
Ono Pharmaceutical Co., Ltd.
Mishima-gun, Osaka 618-8585 (JP)

(74) Representative:
Bentham, Andrew et al
J.A. Kemp & Co.
14 South Square
Gray's Inn
London WC1R 5LX (GB)

(54) **AMIDINO DERIVATIVES AND DRUGS CONTAINING THE SAME AS THE ACTIVE INGREDIENT**

(57) The novel amidino derivatives of the formula (I):



wherein all the symbols are as in specification defined;

EP 1 078 917 A1

EP 1 078 917 A1

have an inhibitory activity of a blood coagulation factor VIIa and are useful for treatment and / or prevention of several angiopathy caused by enhancing a coagulation activity, such as disseminated intravascular coagulation, coronary thrombosis, cerebral infarction, cerebral embolism, transient ischemic attack, cerebrovascular disorders, pulmonary vascular diseases, deep venous thrombosis, peripheral arterial obstruction, thrombosis after artificial vascular transplantation and artificial valve transplantation, post-operative thrombosis, reobstruction and restenosis after coronary artery bypass operation, reobstruction and restenosis after PTCA or PTCR, thrombosis by extracorporeal circulation and procoagulative diseases such as glomerulonephritis.

Description

Technical Field

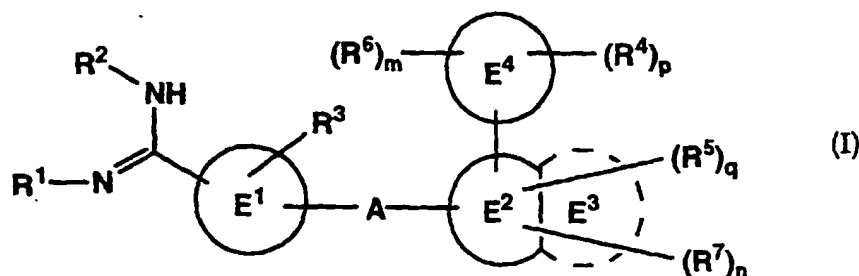
5 [0001] This invention is related to amidino derivatives of the formula (I), non-toxic salts thereof, hydrates thereof, processes for the preparation thereof, and the blood coagulation factor VIIa inhibitors containing the derivatives as active ingredient.

[0002] More particularly, this invention is related to amidino derivatives of the formula (I) :

10

15

20



wherein all the symbols are as hereinafter defined, non-toxic salts thereof, hydrates thereof, processes for the preparation thereof, and the blood coagulation factor VIIa inhibitors containing the derivatives as active ingredient.

25

Background Art

[0003] The blood coagulation is a protective reaction which is caused by vascular injury or irritate stimulus with endotoxin or the other foreign bodies. This reaction proceeds on the membrane of platelets which aggregate at the injured site or on the membrane of injured endothelial cells and it requires Ca ion. The blood coagulation system contains eight kinds of serine proenzymes (e.g. plasma prekallikrein, factor XII, factor XI, factor VII, factor IX, factor X, prothrombin, protein C), five protein co-factor (e.g. macromolecule kininogen, tissue factor, factor VIII, factor V, protein S), and a fibrillar protein, fibrinogen. α -Thrombin produced by the coagulation cascade give information to endothelial cells and form insoluble fibrin gel. The scheme of the blood coagulation cascade is shown below.

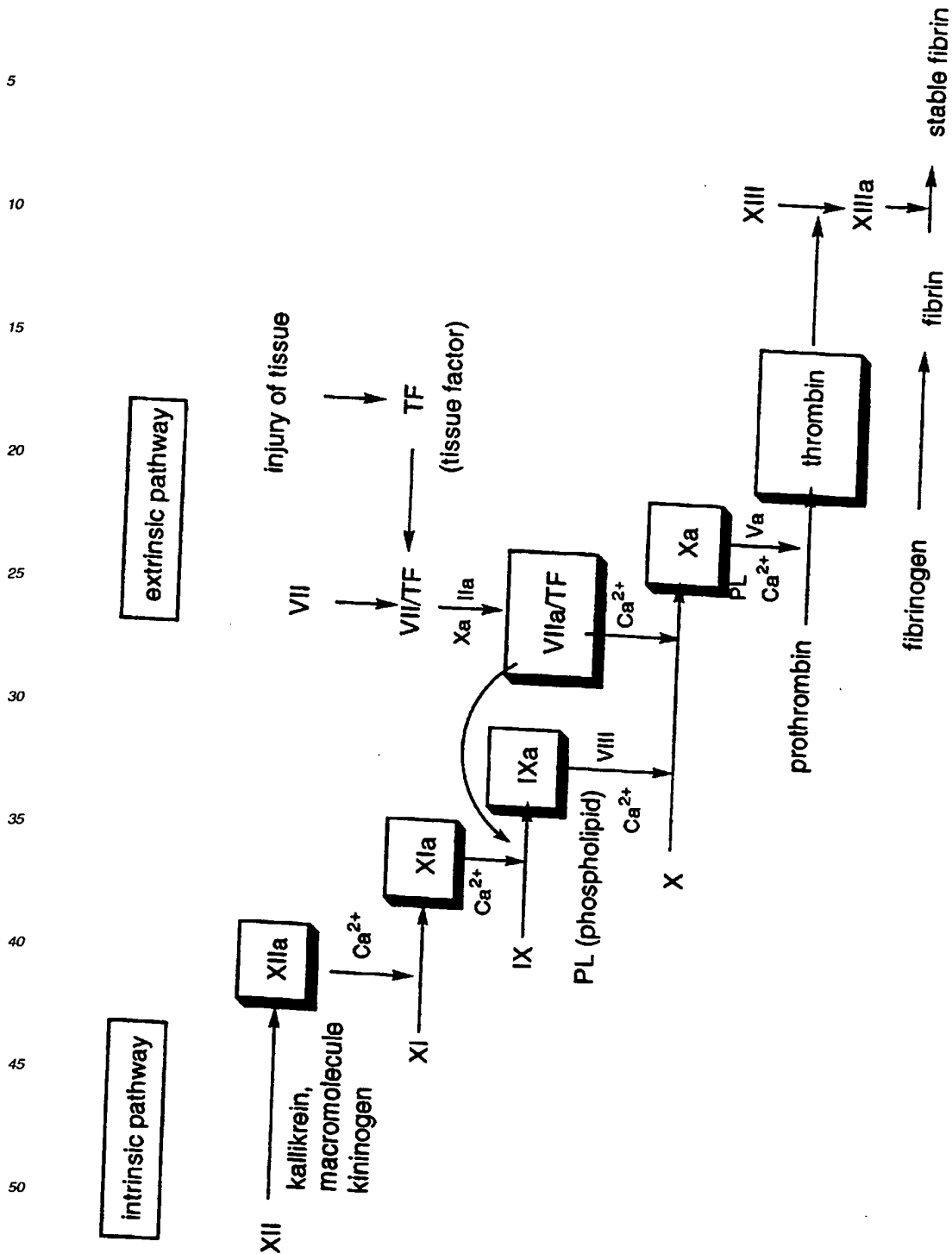
35

40

45

50

55



[0004] The blood coagulation cascade consists of the intrinsic pathway and the extrinsic pathway. The intrinsic pathway acts on foreign surface charged negatively. However, foreign surface in the body is uncertain, so the significance of the intrinsic pathway in hemostasis is not established. On the other hand, the extrinsic pathway is triggered by

the complex formation of the blood coagulation factor VIIa (FVIIa) and tissue factor which is expressed by a vascular damage or the presence of endotoxin. This pathway confluent with the intrinsic pathway at a point of factor X and factor IX activation.

[0005] The extrinsic pathway seems to be more important than the intrinsic pathway in the physiologic condition (hemostasis) or pathological condition (thrombosis). The reasons are as follows.

- 1) The presence of tissue factor (TF) is recognized in physiological condition.
- 2) The expression of TF is induced by endotoxin on the membrane of vascular endothelial cells or/and monocytes.
- 3) Since TF is observed on foam cells in the plaque of arteriosclerosis, the extrinsic pathway is considered to contribute the topical coagulation activity.

[0006] Warfarin, an anticoagulant agent, inhibits the production of various factors, including protein C and S. Thrombin inhibitors such as heparin, which act at the downstream of a coagulation cascade, may inhibit blood coagulation excessively and do not inhibit the consumption of coagulation factors. Because of these reasons, bleeding tendency is the main problem in clinic.

[0007] On the other hand, FVIIa is located at the top site of the cascade in the extrinsic pathway. Therefore, FVIIa inhibitors inhibit the extrinsic pathway, leaving intact the activity of the intrinsic pathway.

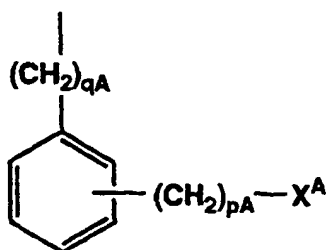
[0008] Consequently, FVIIa inhibitors are different from thrombin inhibitors leaving a function of the intrinsic pathway. It is considered that FVIIa inhibitors have a resistance to bleeding, then it is expected to be able to reduce a bleeding tendency as a side effect.

[0009] FVIIa inhibitors suppress a coagulation activity of the extrinsic pathway, and then they are useful for treatment and / or prevention for several thrombotic diseases triggered by the extrinsic pathway. For example, several angiodysplasia caused by enhancing a coagulation activity, such as disseminated intravascular coagulation, coronary thrombosis (e.g. acute myocardial infarction, unstable angina), cerebral infarction, cerebral embolism, transient ischemic attack, cerebrovascular disorders, pulmonary vascular diseases (e.g. pulmonary infarction, pulmonary embolism), deep venous thrombosis, peripheral arterial obstruction, thrombosis after artificial vascular transplantation and artificial valve transplantation, post-operative thrombosis, reobstruction and restenosis after coronary artery bypass operation, reobstruction and restenosis after PTCA (percutaneous transluminal coronary angioplasty) or PTCR (percutaneous transluminal coronary recanalization), thrombosis by extracorporeal circulation and procoagulative diseases such as glomerulonephritis.

(1) In the specification of WO 9620689, boric acid derivatives of the formula (A) :

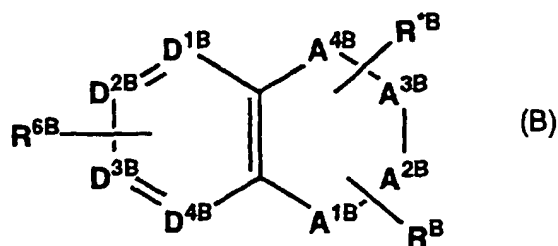


wherein A^A is $-BY^{1A}Y^{2A}$, in which Y^{1A} and Y^{2A} each independently, is $-OH$, C1-8 alkoxy; $-COOR^{3A}$, in which R^{3A} is hydrogen, C1-8 alkyl; R^{2A} is



in which pA is 0-2, qA is 0-4, X^A is $C(NH)NHR^{14A}$, in which R^{14A} is hydrogen, C1-4 alkyl; Z^A is $(CH_2)_{mA}CONR^{8A}$, $(CH_2)_{mA}CSNR^{8A}$, $(CH_2)_{mA}SO_2NR^{8A}$, $(CH_2)_{mA}CO_2$, $(CH_2)_{mA}CSO$, $(CH_2)_{mA}SO_2O$, R^{8A} is hydrogen, C1-8 alkyl, mA is 0-6, R^{1A} is $(CH_2)_{pA}$ aryl, in which pA is 0-2, aryl is phenyl, naphthyl, biphenyl, and they may be substituted by 1-3 of $(CH_2)_{wA}CO_2R^{8A}$, $(CH_2)_{wA}CNR^{8A}R^{9A}$; wA is 0-5, R^{8A} and R^{9A} is hydrogen, C1-8 alkyl; with the proviso that explanations of each groups were disclosed only necessary parts; are described to possible an inhibitory activity of thrombin, Fxa, FVIIa.

(2) In the specification of WO 9429273, the compound of the formula (B):



15 wherein A^{1B} to A^{4B} form a substituted 6 membered ring optionally unsaturated, and optionally containing up to two hetero atoms selected from O, S and N ;

D^{1B} to D^{4B} form a substituted 6 membered aromatic ring optionally containing up to two nitrogens, D^{1B} - D^{4B} is CR^{11B} or N ; R^B is at least one substituent selected from R⁷, Q^B-C1-4 alkyl, Q^B-C2-4 alkenyl and Q^B-C2-4 alkynyl ;

R^{6B} is hydrogen, Q^B-C1-6 alkyl, Ar^B or Het^B ;

Q^B is hydrogen, C3-6 cycloalkylHet^B or Ar^B ;

R^{6B} is W^B-(CR^{B2})^{qB}-Z^B-(CR^BR^{10B})^{rB}-U^B-(CR^{B2})^{sB}-V^B ;

R^{7B} is -COR^{8B}, -PO(OR^B)₂ and Tet^B ;

R^{8B} is -OR^B, -NR^BR^{nB}, -NR^BOR^B ;

R^{10B} is hydrogen, C1-4 alkyl or -NR^BR^{nB} ;

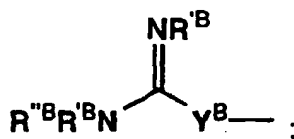
R^{11B} is Q^B-C0-6 alkyl ;

R^B, R^{nB} are hydrogen, C1-6 alkyl, C3-7 cycloalkyl-C0-4 alkyl, or Ar^B-C0-4 alkyl ;

UB and VB is absent or CONR^B, NR^BCO, S(O)_{nB}NR^B, NR^BS(O)_{nB}, NR^BCR^B₂, CR^B₂NR^B, CR^B₂O, OCR^B₂,

C≡C, CR^B=CR^B ;

W^B is



Y^B is absent, S or O ;

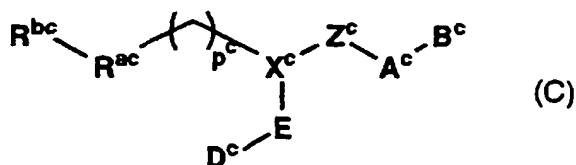
Z^B is (CH₂)_{tB}, Het^B, Ar^B or C3-7 cycloalkyl ;

nB is 0-3 ; qB is 0-3 ; rB is 0-2 ; sB is 0-2 ; tB is 0-2 ; with the proviso that explanations of each groups were disclosed only necessary parts;

or salts thereof are described to possible an inhibitory activity of fibrinogen receptor GPIIb/IIIa.

In the specification of WO 9300095 and WO 9412478, similarity compounds are described to possible an inhibitory activity of fibrinogen receptor GPIIb/IIIa.

(3) In the specification of WO 9730971, the compound of the formula (C):

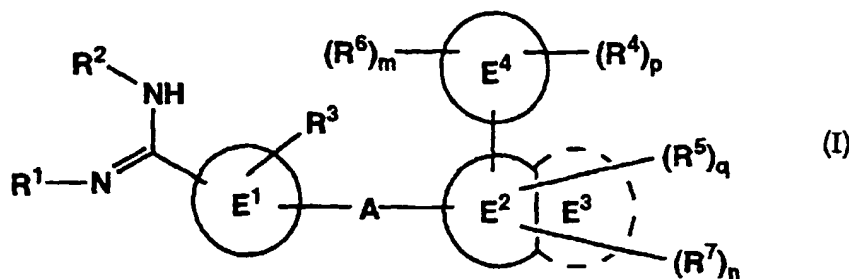


wherein D^c is CN, $C(=NR^{7c})NR^{8c}R^{9c}$, $NHC(=NR^{7c})NR^{8c}R^{9c}$, $NR^{8c}CH(=NR^{7c})$ etc.; E^c is phenyl, 2-pyridyl, 4-pyridyl, etc.; R^{ac} is a single bond or $CH=CH$; R^{bc} is $C(O)R^c$ or G^c ; G^c is hydrogen, OG^{1c} , SG^{1c} , $NG^{1c}G^{2c}$, etc.; G^{1c} is hydrogen, C1-6 alkyl; G^{2c} is hydrogen, C1-6 alkyl; R^c is hydrogen, OH, C1-6 alkoxy, etc.; R^{7c} is hydrogen, OH, C1-6 alkyl, C1-6 alkylcarbonyl, C1-6 alkoxy, C1-4 alkoxy carbonyl, etc.; R^{8c} and R^{9c} are hydrogen, C1-6 alkyl, $(CH_2)_n$ -phenyl; X^c is $CHCH(R^{1c})$, N, etc.; Z^c is $(CH_2)_n$, $C(=O)$, etc.; p^c is 1-4; A^c is benzyl, C3-10 carbocyclic ring, 5-10 membered heterocyclic ring; B^c is hydrogen, C1-6 alkyl, benzyl, C3-10 carbocyclic ring, 5-10 membered heterocyclic ring; are described to possess an inhibitory activity of FXa.

Disclosure of Invention

[0010] Energetic investigations have been carried out in order to make the blood coagulation factor VIIa inhibitors. The present inventors have found that the present compound of the formula (I) accomplished the present purpose.

[0011] The present invention is related to amidino derivatives of the formula (I):



wherein R^1 and R^2 each independently, is

- 1) hydrogen,
 - 2) hydroxy,
 - 3) C1-4 alkoxy carbonyl,
 - 4) C2-4 alkenyloxy carbonyl,
 - 5) C1-4 alkoxy carbonyloxy or
 - 6) $-COO-(C1-4 \text{ alkyl})\text{-phenyl}$,
- with the proviso that when R^1 is group excepting hydrogen, R^2 is hydrogen, or when R^2 is group excepting hydrogen, R^1 is hydrogen;

R^3 is

- 1) hydrogen,
- 2) C1-4 alkyl,
- 3) hydroxy,
- 4) $-O-(C1-4 \text{ alkyl})\text{-phenyl}$, or
- 5) halogen atom;

E¹ ring is

- 1) 5-7 membered unsaturated carbocyclic ring or
- 2) 5-7 membered unsaturated heterocyclic ring ;

E² ring is

- 1) 5-7 membered unsaturated carbocyclic ring or
- 2) 5-7 membered unsaturated heterocyclic ring ;

E³ ring is

- 1) absent,
- 2) 5-7 membered unsaturated or saturated carbocyclic ring or
- 3) 5-7 membered unsaturated or saturated heterocyclic ring ;

E⁴ ring is

- 1) 5-6 membered unsaturated carbocyclic ring or
- 2) 5-6 membered unsaturated heterocyclic ring ;

R⁴ and R⁵ each independently, is

- 1) -COOR⁸, in which R⁸ is hydrogen, C1-8 alkyl, -(C1-4 alkyl)-phenyl or -(C1-4 alkyl)-O-(C1-4 alkyl) ;
 - 2) -(C1-4 alkyl)-COOR⁹, in which R⁹ is hydrogen, C1-8 alkyl, -(C1-4 alkyl)-phenyl or -(C1-4 alkyl)-O-(C1-4 alkyl) ;
 - 3) -(C2-4 alkenyl)-COOR¹⁰, in which R¹⁰ is hydrogen, C1-8 alkyl, -(C1-4 alkyl)-phenyl or -(C1-4 alkyl)-O-(C1-4 alkyl) ;
 - 4) -O-(C1-4 alkyl)-COOR¹¹, in which R¹¹ is hydrogen, C1-8 alkyl, -(C1-4 alkyl)-phenyl or -(C1-4 alkyl)-O-(C1-4 alkyl) ;
 - 5) -CONR¹²R¹³, in which R¹² is hydrogen, C1-4 alkyl, R¹³ is hydroxy, -O-(C1-4 alkyl)-phenyl or cyano ;
 - 6) -P(O)(OR¹⁴)₂, in which R¹⁴ is hydrogen, C1-4 alkyl or -(C1-4 alkyl)-phenyl ; or
 - 7) tetrazol-5-yl which is optionally substituted by C1-8 alkyl ;
- p and q each independently, is 0 or 1-2, with the proviso that p + q is 1 or 2 ;

R⁶ and R⁷ each independently, is

- 1) hydrogen,
- 2) C1-8 alkyl,
- 3) nitro,
- 4) cyano,
- 5) halogen atom,
- 6) -(C1-4 alkyl)-O-(C1-4 alkyl)-phenyl,
- 7) -NR¹⁵R¹⁶, in which R¹⁵ and R¹⁶ each independently, is hydrogen or C1-8 alkyl ;
- 8) -OR¹⁷, in which R¹⁷ is hydrogen, C1-8 alkyl, CF₃, C2-5 acyl, -(C1-4 alkyl)-phenyl, -(C1-4 alkyl)-OH, -(C1-4 alkyl)-O-(C1-4 alkyl), or -(C1-4 alkyl)-O-(C1-4 alkyl)-O-(C1-4 alkyl) ;
- 9) -(C1-4 alkyl)-OR¹⁷, in which R¹⁷ is as hereinbefore defined ;
- 10) -J¹-J², in which J¹ is

- (1) -CONR¹⁸-, in which R¹⁸ is hydrogen or C1-4 alkyl ;
- (2) -NR¹⁹CO-, in which R¹⁹ is hydrogen or C1-4 alkyl ;
- (3) -SO₂NR²⁰-, in which R²⁰ is hydrogen or C1-4 alkyl ;
- (4) -NR²¹SO₂-, in which R²¹ is hydrogen or C1-4 alkyl ;
- (5) -(C1-4 alkyl)-NR²²-, in which R²² is hydrogen or C1-4 alkyl ;
- (6) -CO-,
- (7) -(C1-4 alkyl)-NR²³CO-, in which R²³ is hydrogen or C1-4 alkyl ;

J² is

(1) C1-15 alkyl optionally substituted by 1-3 of following groups (i) - (x):

- (i) C3-7 cycloalkyl optionally substituted by -(C1-4 alkyl)-OR²⁴ ;
- (ii) phenyl,
- (iii) 5-7 saturated heterocyclic ring optionally substituted by carboxyl or C1-4 alkoxy carbonyl ;
- (iv) OR²⁴, in which R²⁴ is hydrogen, C1-4 alkyl, -COO-(C1-4 alkyl)-phenyl, C2-5 acyl, or -(C1-4 alkyl)-phenyl ;
- (v) NR²⁵R²⁶, in which R²⁵ is hydrogen or C1-4 alkyl, R²⁶ is hydrogen, C1-4 alkyl, -COO(C1-4 alkyl)-phenyl, imino(C1-4 alkyl) or C1-4 alkoxy carbonyl ;
- (vi) -S(O)_r-(C1-4 alkyl), in which r is 0-2 ;
- (vii) -COOR²⁷, in which R²⁷ is hydrogen, C1-4 alkyl or -(C1-4 alkyl)-phenyl ;
- (viii) -CONR²⁸R²⁹, in which R²⁸ and R²⁹ each independently, is
 - (i) hydrogen, (ii) C1-4 alkyl, (iii) hydroxy, or (iv) C1-4 alkyl substituted by one of hydroxy, phenyl or NR²⁵R²⁶, or R²⁸ and R²⁹ taken together with the nitrogen atom to which they are attached form 5-6 membered saturated heterocyclic ring containing nitrogen atom ;
- (ix) halogen atom,
- (x) trihalomethyl ;

- (2) C2-8 alkenyl,
- (3) C5-7 cycloalkyl optionally substituted by 1-3 of C1-4 alkyl, -COOR²⁷, in which R²⁷ is as hereinbefore defined; -(C1-4 alkyl)-OR²⁴, in which R²⁴ is as hereinbefore defined;
- (4) -NR²⁵R²⁶, in which R²⁵ and R²⁶ is as hereinbefore defined;
- (5) 5-6 membered saturated heterocyclic ring optionally substituted by 1-3 of C1-4 alkyl, oxo, imino(C1-4 alkyl) ; or R¹⁸ and J² taken together with the nitrogen atom to which they are attached form saturated heterocyclic ring optionally substituted by 1-3 of C1-8 alkyl, C2-8 alkenyl or -COOR²⁷, in which R²⁷ is as hereinbefore defined;

m is 1-3;

n is 1-3;

two R⁶ taken together with the neighboring two carbon of E⁴ ring to which they are attached form 5-6 membered unsaturated carbocyclic ring or 5-6 membered saturated heterocyclic ring, that rings may be substituted by 1-3 of R⁴ or R⁶;

A is

- 1) ethylene,
- 2) vinylene,
- 3) ethynylene,
- 4) -O-CH₂-,
- 5) -CH₂-O-,
- 6) -NR³⁰CO-, in which R³⁰ is hydrogen or C1-4 alkyl ;
- 7) -NR³¹CHR³²-, in which R³¹ is hydrogen or C1-4 alkyl, R³² is hydrogen, cyano, COOR³⁶, in which R³⁶ is hydrogen or C1-4 alkyl; or CONR³⁷R³⁸, in which R³⁷ and R³⁸ each independently, is hydrogen or C1-4 alkyl ;
- 8) -CH₂-NR³³-, in which R³³ is hydrogen or C1-4 alkyl ;
- 9) -S-CH₂-,
- 10) -CH₂-S-,
- 11) -SO₂NR³⁴-, in which R³⁴ is hydrogen or C1-4 alkyl ;
- 12) -NR³⁵SO₂-, in which R³⁵ is hydrogen or C1-4 alkyl ;
- non-toxic salts thereof, or hydrates thereof,

(2) the blood coagulation factor VIIa inhibitors containing the compound of formula (I) as active ingredient,

(3) processes for the preparation of the compound of formula (I).

Detailed description of Invention

[0012] Unless otherwise specified, all isomers are included in the present invention. For example, alkyl, alkoxy and alkylene include straight and branched isomers. Isomers based on double bond, ring, fused ring (E, Z, cis, trans), iso-

mers resulting from the presence of asymmetric carbon(s) (R-configuration, S-configuration, α -configuration, β -configuration, enantiomers, diastereoisomers), optically active compound having optical rotation (D, L, d, l-configuration), polar compounds obtained by chromatographic separations (high polar compound, low polar compound), equilibrium compounds, the mixtures are existed by free ratio, racemic mixtures are included in the present invention.

5 **[0013]** In the compound of the formula (I),

C1-4 alkyl represented by $R^3, R^{12}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22}, R^{23}, R^{24}, R^{25}, R^{26}, R^{27}, R^{28}, R^{29}, R^{30}, R^{31}, R^{33}, R^{34}, R^{35}, R^{36}, R^{37}, R^{38}$,

C1-4 alkyl in -COO-(C1-4 alkyl)-phenyl represented by R^1, R^2, R^{24}, R^{26} ,

10 C1-4 alkyl in -O-(C1-4 alkyl)-phenyl represented by R^3, R^{13} ,

C1-4 alkyl in -(C1-4 alkyl)-phenyl represented by $R^8, R^9, R^{10}, R^{11}, R^{14}, R^{17}, R^{27}, R^{28}, R^{29}$,

C1-4 alkyl in -(C1-4 alkyl)-O-(C1-4 alkyl) represented by $R^8, R^9, R^{10}, R^{11}, R^{17}$,

C1-4 alkyl in -(C1-4 alkyl)-COOR⁹ represented by R^4, R^5 ,

C1-4 alkyl in -O-(C1-4 alkyl)-COOR¹¹ represented by R^4, R^5 ,

15 C1-4 alkyl in -(C1-4 alkyl)-O-(C1-4 alkyl)-phenyl represented by R^6, R^7 ,

C1-4 alkyl in -(C1-4 alkyl)-OH represented by R^{17}, R^{28}, R^{29} ,

C1-4 alkyl in -(C1-4 alkyl)-O-(C1-4 alkyl)-O-(C1-4 alkyl) represented by R^{17} ,

C1-4 alkyl in -(C1-4 alkyl)-NR²² represented by J^1 ,

C1-4 alkyl in -(C1-4 alkyl)-NR²³CO- represented by J^1 ,

20 C1-4 alkyl in -S(O)_r-(C1-4 alkyl) represented in J^2 ,

C1-4 alkyl in J^2 ,

C1-4 alkyl in -(C1-4 alkyl)-R²⁴ represented in J^2 ,

C1-4 alkyl in -imino(C1-4 alkyl) represented in J^2 and by R^{26} ,

C1-4 alkyl in -(C1-4 alkyl)-OR¹⁷ represented by R^6, R^7 ,

25 C1-4 alkyl in -(C1-4 alkyl)-NR²⁵R²⁶ represented by R^{28}, R^{29} is methyl, ethyl, propyl, butyl and isomeric groups thereof.

[0014] C1-8 alkyl represented by $R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{15}, R^{16}, J^2$, C1-8 alkyl as substituents of heterocyclic ring containing nitrogen atom and tetrazol ring represented by R^4, R^5 is methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl and isomeric groups thereof.

[0015] C1-4 alkoxy in C1-4 alkoxycarbonyl represented by R^1, R^2 , C1-4 alkoxy in C1-4 alkoxycarbonyloxy represented by R^1, R^2 , C1-4 alkoxy in C1-4 alkoxycarbonyl as substituents of 5-7 membered saturated heterocyclic ring represented by J^2 is methoxy, ethoxy, propoxy, butoxy and isomeric groups thereof.

[0016] C2-4 alkenyl in C2-4 alkenyloxycarbonyl represented by R^1, R^2 , C2-4 alkenyl in -(C2-4 alkenyl)-COOR¹⁰ represented by R^4, R^5 is ethenyl, propenyl, butenyl and isomeric groups thereof.

[0017] Halogen atom represented by R^6, R^7 is fluorine, chlorine, bromine or iodine.

[0018] Trihalomethyl in J^2 is methyl substituted by 3 of halogen atoms that is fluorine, chlorine, bromine or iodine.

[0019] C3-7 cycloalkyl as substituents in J^2 is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl.

[0020] C5-7 cycloalkyl as substituents in J^2 is cyclopentyl, cyclohexyl or cycloheptyl.

40 **[0021]** C2-5 acyl represented by R^{17}, R^{24} is acetyl, propionyl, butyryl, valeryl and isomeric groups thereof.

[0022] 5-7 membered unsaturated carbocyclic ring represented by E^1, E^2, E^3 is cyclopentadiene, benzene, cycloheptatriene etc.

[0023] 5-7 membered saturated carbocyclic ring represented by E^3 is cyclopentane, cyclohexane, cycloheptane.

[0024] 5-6 membered unsaturated carbocyclic ring represented by E^4 , and 5-6 membered unsaturated carbocyclic ring formed by two R^6 is cyclopentadiene, benzene.

[0025] 5-7 membered unsaturated or saturated heterocyclic ring represented by E^1, E^2, E^3 , 5-7 membered saturated heterocyclic ring in J^2 , means 5-7 membered unsaturated or saturated heterocyclic ring containing 1-2 of hetero atom(s) selected by oxygen, sulfur and / or nitrogen.

[0026] For example, 5-7 membered unsaturated or saturated heterocyclic ring containing 1-2 of hetero atom(s) selected by oxygen, sulfur and / or nitrogen is pyrroline, pyrrolidine, imidazoline, imidazolidine, pyrazoline, pyrazolidine, piperidine, piperazine, tetrahydropyrimidine, hexahydropyrimidine, tetrahydropyridazine, hexahydropyridazine, hexahydroazepine, dihydrofuran, tetrahydrofuran, dihydropyran, tetrahydropyran, dihydrothiophene, tetrahydrothiophene, dihydrothiain (dihydrothiopyran), tetrahydrothiain (tetrahydrothiopyran), dihydrooxazole, tetrahydrooxazole, dihydroisoxazole, tetrahydroisoxazole, dihydrothiazole, tetrahydrothiazole, dihydroisothiazole, tetrahydroisothiazole, morpholine, thiomorpholine, pyrrole, imidazole, pyrazole, pyridine, pyrazine, pyrimidine, pyridazine, azepine, diazepine, furan, pyran, oxepin, oxazepine, thiophene, thian (thiopyran), thiepin, oxazole, isoxazole, thiazole, isothiazole, oxadiazole, oxazine, oxadiazine, oxazepine, oxadiazepine, thiadiazole, thiazine, thiadiazine, thiazepine, thiadiazepine.

[0027] 5-6 membered unsaturated heterocyclic ring represented by E^4 means 5-6 membered saturated heterocyclic-

clic ring containing one of oxygen, sulfur or nitrogen, for example, furan, thiophene, pyrrole, pyridine.

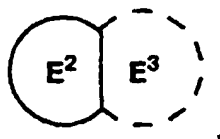
[0028] 5-6 membered saturated heterocyclic ring represented by J^2 means 5-6 membered saturated heterocyclic ring containing 1-2 of hetero atom(s) selected by oxygen atom, sulfur atom and / or nitrogen atom, for example, oxolane, oxane, pyrrolidine, piperidine, dioxolane, dioxane, imidazolidine, pyrazolidine, piperazine, morpholine.

- 5 **[0029]** A saturated heterocyclic ring containing nitrogen formed by R^{18} and J^2 taken together with the nitrogen atom to which they are attached, or R^{28} and R^{29} taken together with the nitrogen atom to which they are attached means 5-6 membered saturated heterocyclic ring containing one nitrogen, two nitrogens, one nitrogen and one oxygen, or one nitrogen and one sulfur, for example, pyrrolidine, piperidine, imidazolidine, pyrazolidine, piperazine, morpholine, thiomorpholine.

- 10 **[0030]** 5-6 membered saturated heterocyclic ring formed by two R^6 taken together with the neighboring two carbon of E^4 ring to which they are attached means 5-6 membered saturated heterocyclic ring containing 1-2 of hetero atom(s) of oxygen, sulfur and / or nitrogen, for example, oxolane, oxane, pyrrolidine, piperidine, thiolane, thiane, dioxolane, dioxane, imidazolidine, pyrazolidine, dithiolane, dithiane, piperazine, oxathiane, morpholine, thiomorpholine.

[0031] In the formula (I), the ring represented by

15



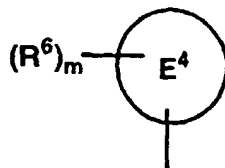
20

means E^3 ring is absent, that is only E^2 ring represents ring, and both of E^2 ring and E^3 ring represent ring, for example, benzene, naphthalene, 1, 2, 3, 4-tetrahydronaphthalene, indan, benzofuran, 2, 3-dihydrobenzofuran, benzoimidazole, 1, 3-dioxaindan, benzothiophene, pyridine, pyrimidine, isoquinoline, thiophene, furan. Especially preferable group is benzene, pyridine, thiophene, furan.

25

[0032] In the formula (I), as ring represented by

30



35

benzene, naphthalene, 2, 3-dihydrobenzofuran, 1, 3-dioxaindan, pyridine, furan, thiophen are preferable. Especially preferable group is benzene, pyridien, furan, thiophene.

- 40 **[0033]** In the formula (I), all groups represented by R^4 and R^5 are preferable. Especially preferable group is $COOR^8$.

[0034] Besides, especially preferable attachment point on E^4 ring of one R^4 is ortho position.

[0035] In the formula (I), all groups represented by R^6 are preferable. Especially preferably, at least one of R^6 is $-J^1-J^2$.

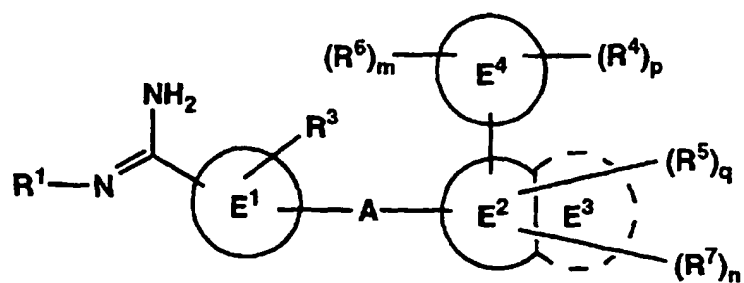
- 45 **[0036]** In the formula (I), all groups represented by R^7 are preferred. Especially preferably, at least one of R^7 is hydrogen, C1-4 alkyl, nitro, $NR^{15}R^{16}$, OR^{17} , $-(C1-4\text{ alkyl})-OR^{17}$.

[0037] In the formula (I), all groups represented by A are preferable. Especially preferable groups are $-CH_2-O-$, $NR^{30}CO-$, $NR^{31}CHR^{32}-$.

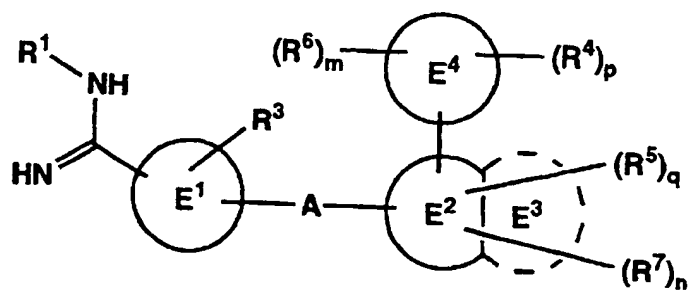
[0038] In the compound of the formula (I), the compound of the formula

50

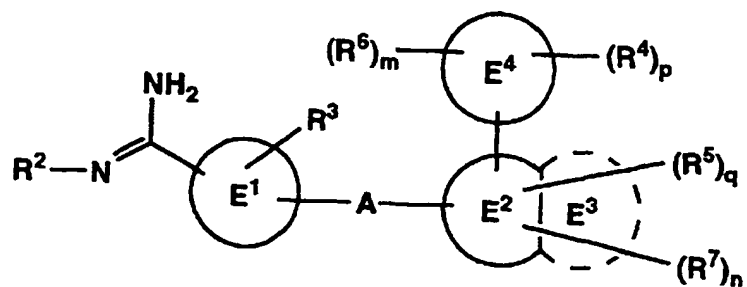
55



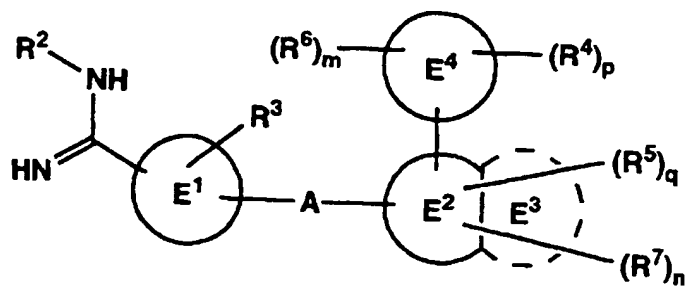
and the compound of the formula



are equivalence, and
the compound of the formula

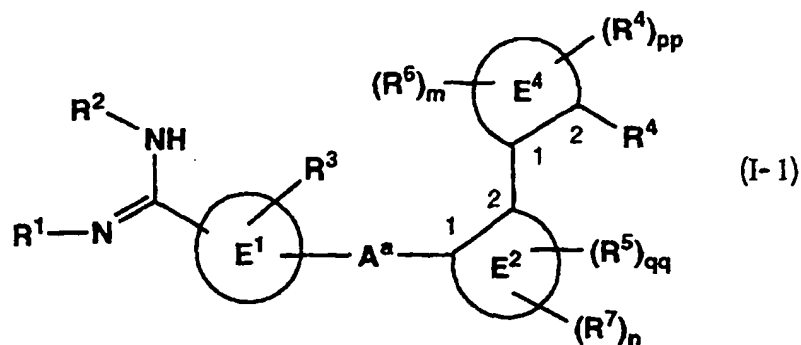


and the compound of the formula



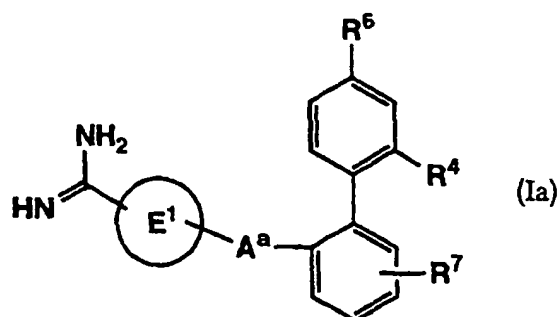
are equivalence.

[0039] In the compounds of the present invention of formulae (I), the compounds of the formula (I-1):

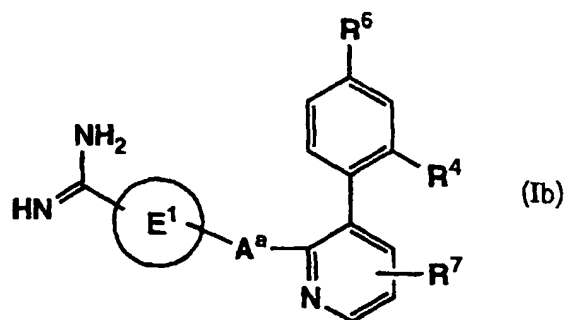


20 wherein A^a is $-\text{CH}_2-\text{O}-$, $-\text{NR}^{30}\text{CO}-$ in which R^{30} is as hereinbefore defined; $-\text{NR}^{31}\text{CHR}^{32}-$ in which R^{31} and R^{32} are as hereinbefore defined; pp and qq each independently, is 0-1, with the proviso that $\text{pp} + \text{qq}$ is 0 or 1, the other symbols are as hereinbefore defined, with the proviso that A^a and E^4 ring attach to E^2 ring at ortho position, E^2 ring and essential one R^4 attach to E^4 ring at ortho position; are preferable.

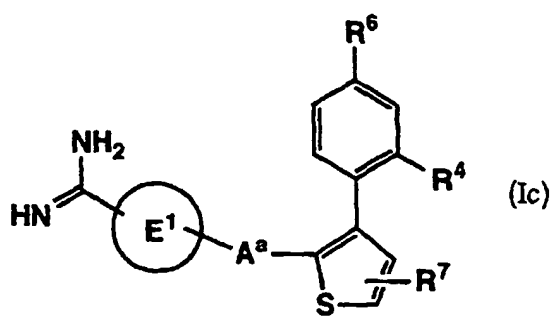
[0040] The following compounds of the formulae are especially preferable: the formula (Ia):



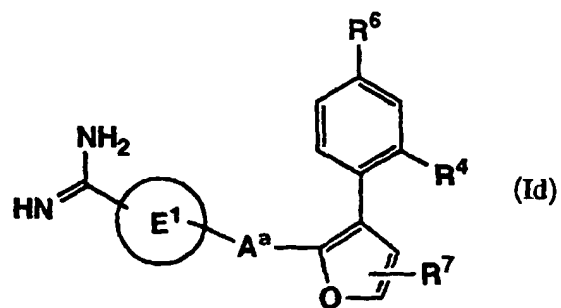
40 wherein all the symbols are as hereinbefore defined;
the formula (Ib):



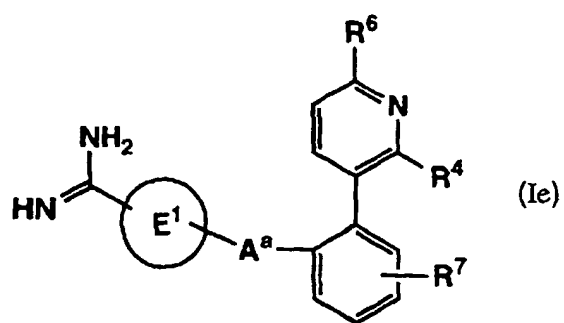
wherein all the symbols are as hereinbefore defined;
the formula (Ic):



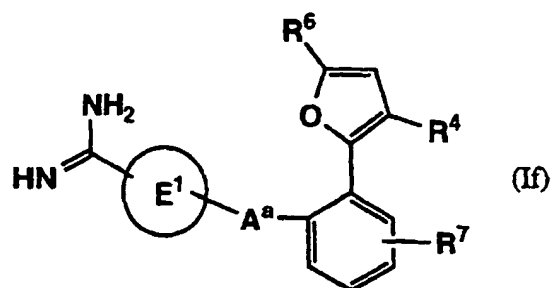
15 wherein all the symbols are as hereinbefore defined;
the formula (Id) :



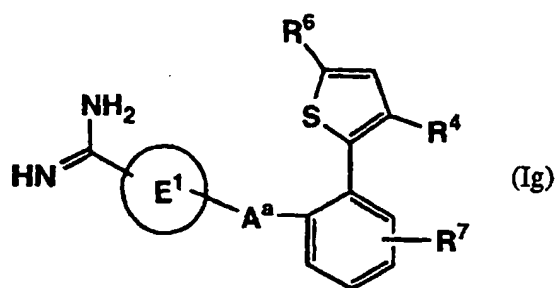
35 wherein all the symbols are as hereinbefore defined;
the formula (Ie) :



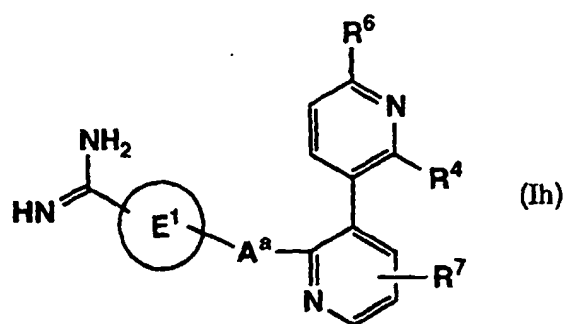
50 wherein all the symbols are as hereinbefore defined;
the formula (If) :



15 wherein all the symbols are as hereinbefore defined;
the formula (lg) :

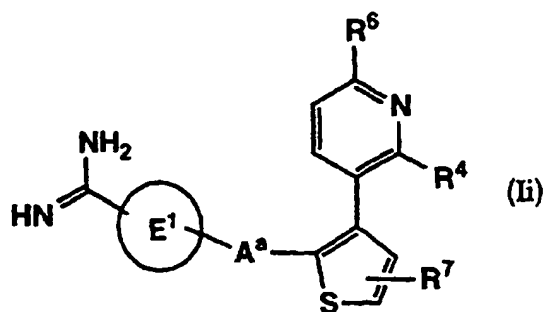


30 wherein all the symbols are as hereinbefore defined;
the formula (lh) :



50 wherein all the symbols are as hereinbefore defined;
the formula (li) :

55

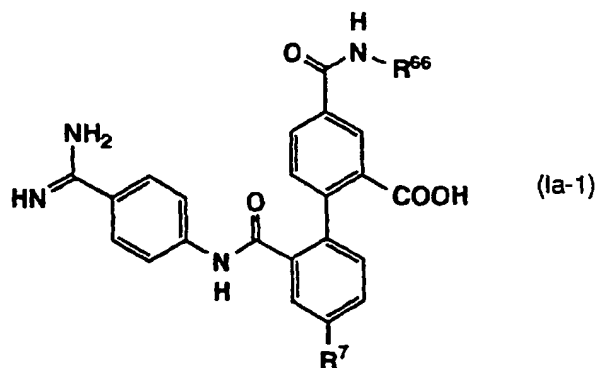


15 wherein all the symbols are as hereinbefore defined;
non-toxic salts thereof, or hydrates thereof.

[0041] As the specific compounds described in Table 1 - Table 27, non-toxic salts thereof and hydrates thereof, and the compounds described in the Examples are preferable.

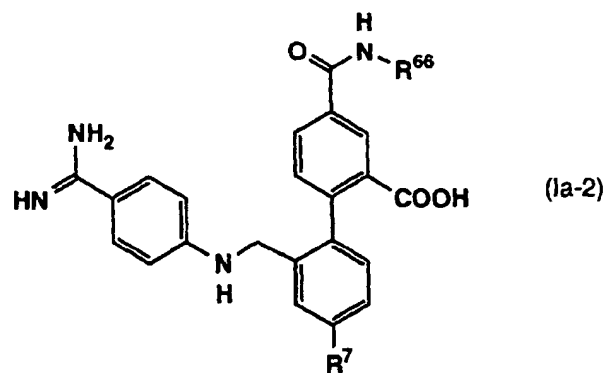
20 [0042] The following compounds include isomers resulting from the presence of asymmetric carbon(s), that is R-configuration, S-configuration and RS-configuration are also included.

Table 1



No.	R ⁷	R ⁶⁶	No.	R ⁷	R ⁶⁶
1	H		10	CH ₃	
2	H		11	CH ₃	
3	H		12	CH ₃	
4	H		13	OCH ₃	
5	H		14	OCH ₃	
6	H		15	OCH ₃	
7	CH ₃		16	OCH ₃	
8	CH ₃		17	OCH ₃	
9	CH ₃		18	OCH ₃	

Table 2




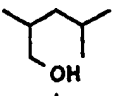

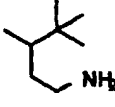
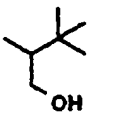
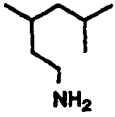
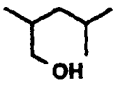

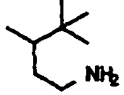

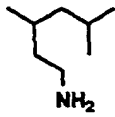
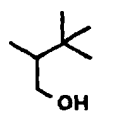

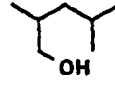

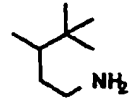
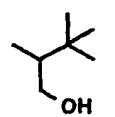
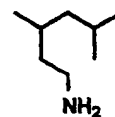
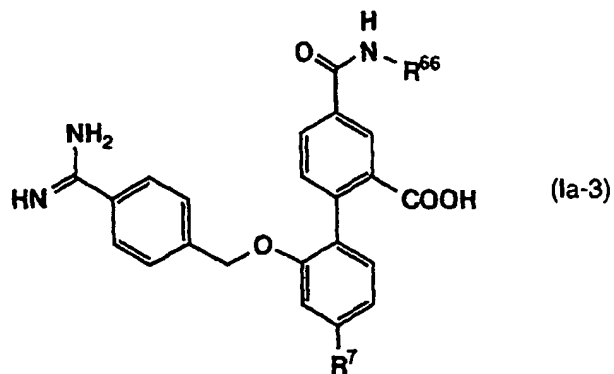
No.	R^7	R^{66}	No.	R^7	R^{66}
1	H		10	CH_3	
2	H		11	CH_3	
3	H		12	CH_3	
4	H		13	OCH_3	
5	H		14	OCH_3	
6	H		15	OCH_3	
7	CH_3		16	OCH_3	
8	CH_3		17	OCH_3	
9	CH_3		18	OCH_3	

Table 3




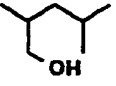

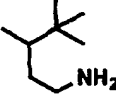
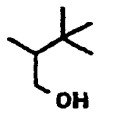
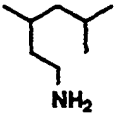
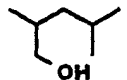

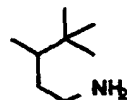
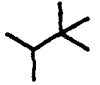
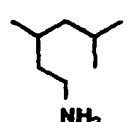
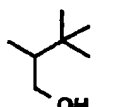

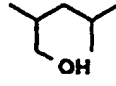

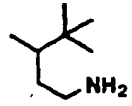
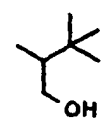
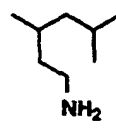
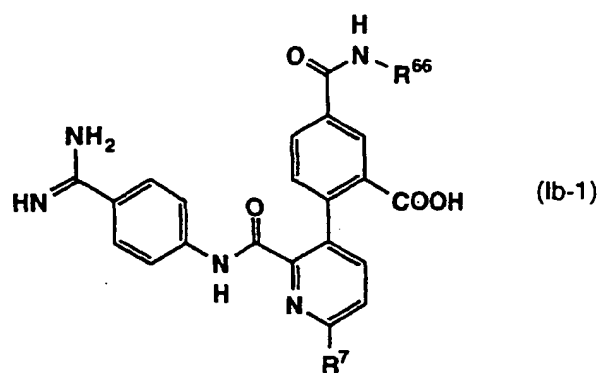
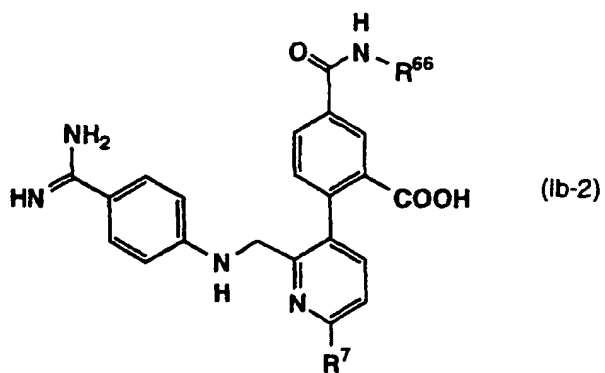
No.	R^7	R^{66}	No.	R^7	R^{66}
1	H		10	CH_3	
2	H		11	CH_3	
3	H		12	CH_3	
4	H		13	OCH_3	
5	H		14	OCH_3	
6	H		15	OCH_3	
7	CH_3		16	OCH_3	
8	CH_3		17	OCH_3	
9	CH_3		18	OCH_3	

Table 4



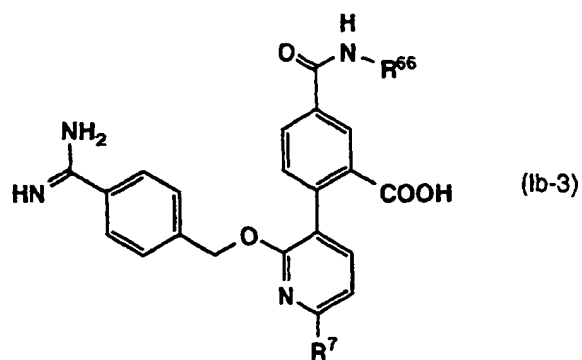
No.	R ⁷	R ⁶⁶	No.	R ⁷	R ⁶⁶
1	H		10	CH ₃	
2	H		11	CH ₃	
3	H		12	CH ₃	
4	H		13	OCH ₃	
5	H		14	OCH ₃	
6	H		15	OCH ₃	
7	CH ₃		16	OCH ₃	
8	CH ₃		17	OCH ₃	
9	CH ₃		18	OCH ₃	

Table 5



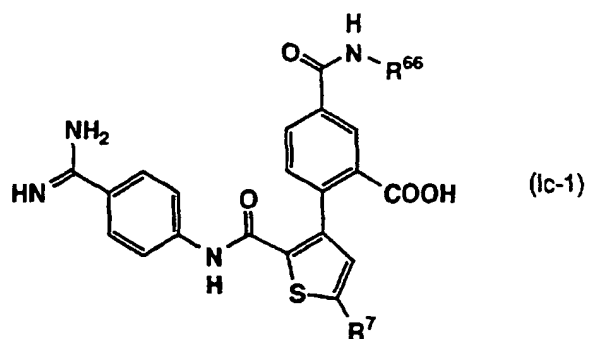
No.	R ⁷	R ⁶⁶	No.	R ⁷	R ⁶⁶
1	H		10	CH ₃	
2	H		11	CH ₃	
3	H		12	CH ₃	
4	H		13	OCH ₃	
5	H		14	OCH ₃	
6	H		15	OCH ₃	
7	CH ₃		16	OCH ₃	
8	CH ₃		17	OCH ₃	
9	CH ₃		18	OCH ₃	

Table 6



No.	R ⁷	R ⁶⁶	No.	R ⁷	R ⁶⁶
1	H		10	CH ₃	
2	H		11	CH ₃	
3	H		12	CH ₃	
4	H		13	OCH ₃	
5	H		14	OCH ₃	
6	H		15	OCH ₃	
7	CH ₃		16	OCH ₃	
8	CH ₃		17	OCH ₃	
9	CH ₃		18	OCH ₃	

Table 7




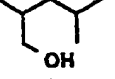

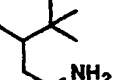
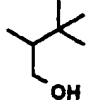
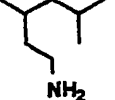
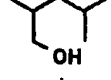

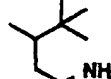

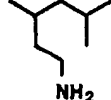
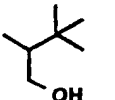

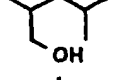

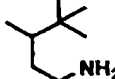
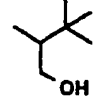
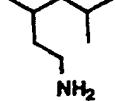
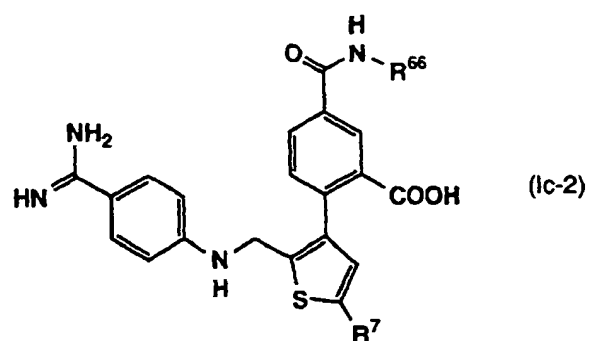
No.	R ⁷	R ⁶⁶	No.	R ⁷	R ⁶⁶
1	H		10	CH ₃	
2	H		11	CH ₃	
3	H		12	CH ₃	
4	H		13	OCH ₃	
5	H		14	OCH ₃	
6	H		15	OCH ₃	
7	CH ₃		16	OCH ₃	
8	CH ₃		17	OCH ₃	
9	CH ₃		18	OCH ₃	

Table 8







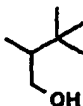
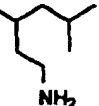
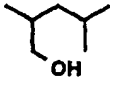

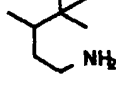

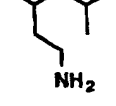
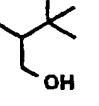




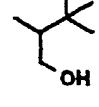
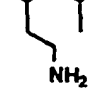
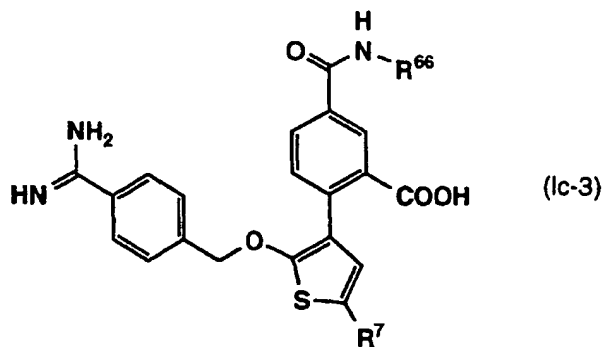
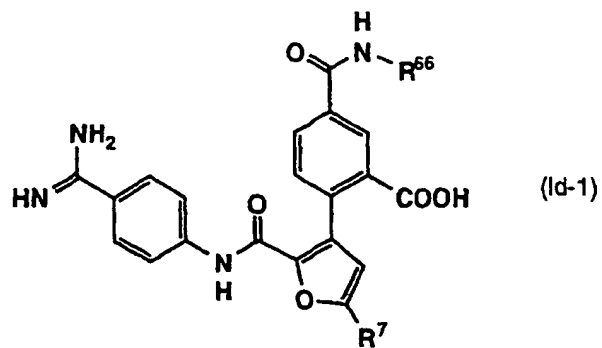
No.	R^7	R^{66}	No.	R^7	R^{66}
1	H		10	CH ₃	
2	H		11	CH ₃	
3	H		12	CH ₃	
4	H		13	OCH ₃	
5	H		14	OCH ₃	
6	H		15	OCH ₃	
7	CH ₃		16	OCH ₃	
8	CH ₃		17	OCH ₃	
9	CH ₃		18	OCH ₃	

Table 9



No.	R ⁷	R ⁶⁶	No.	R ⁷	R ⁶⁶
1	H		10	CH ₃	
2	H		11	CH ₃	
3	H		12	CH ₃	
4	H		13	OCH ₃	
5	H		14	OCH ₃	
6	H		15	OCH ₃	
7	CH ₃		16	OCH ₃	
8	CH ₃		17	OCH ₃	
9	CH ₃		18	OCH ₃	

Table 10




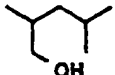

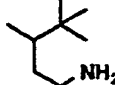
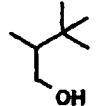
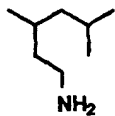
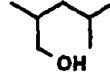

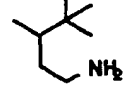

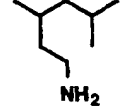
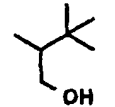

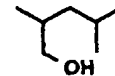

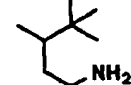
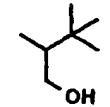
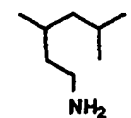
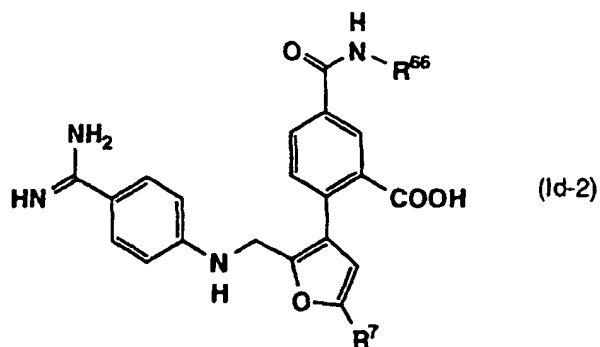
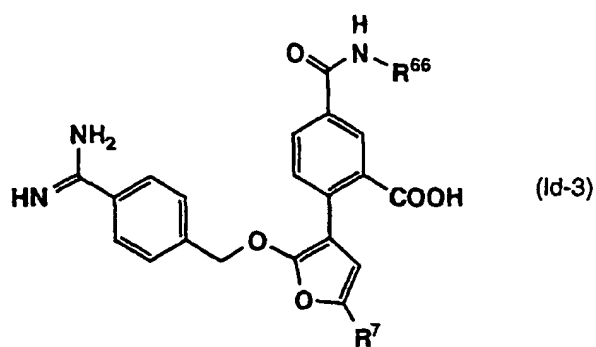
No.	R ⁷	R ⁶⁶	No.	R ⁷	R ⁶⁶
1	H		10	CH ₃	
2	H		11	CH ₃	
3	H		12	CH ₃	
4	H		13	OCH ₃	
5	H		14	OCH ₃	
6	H		15	OCH ₃	
7	CH ₃		16	OCH ₃	
8	CH ₃		17	OCH ₃	
9	CH ₃		18	OCH ₃	

Table 11



No.	R ⁷	R ⁶⁶	No.	R ⁷	R ⁶⁶
1	H		10	CH ₃	
2	H		11	CH ₃	
3	H		12	CH ₃	
4	H		13	OCH ₃	
5	H		14	OCH ₃	
6	H		15	OCH ₃	
7	CH ₃		16	OCH ₃	
8	CH ₃		17	OCH ₃	
9	CH ₃		18	OCH ₃	

Table 12




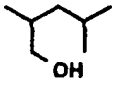

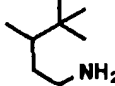
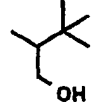
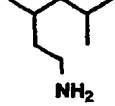
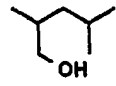

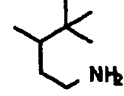

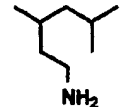
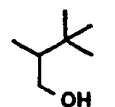

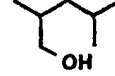

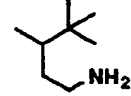
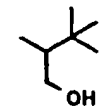
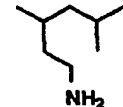
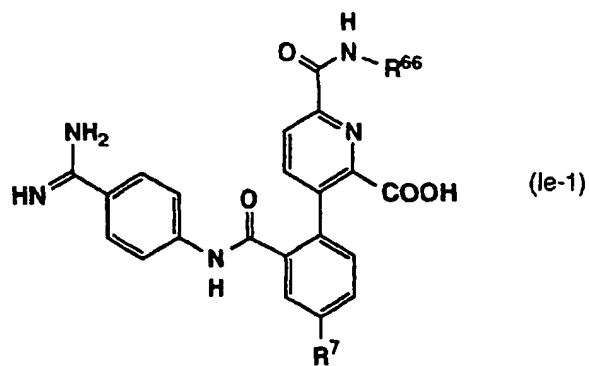
No.	R ⁷	R ⁶⁶	No.	R ⁷	R ⁶⁶
1	H		10	CH ₃	
2	H		11	CH ₃	
3	H		12	CH ₃	
4	H		13	OCH ₃	
5	H		14	OCH ₃	
6	H		15	OCH ₃	
7	CH ₃		16	OCH ₃	
8	CH ₃		17	OCH ₃	
9	CH ₃		18	OCH ₃	

Table 13




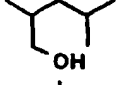
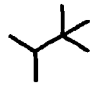
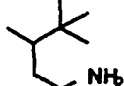
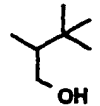
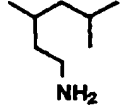
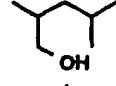

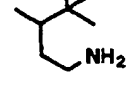
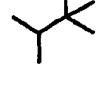
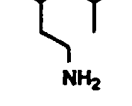
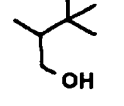

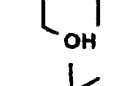
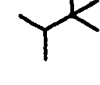
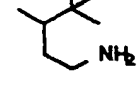
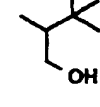
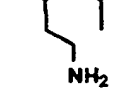
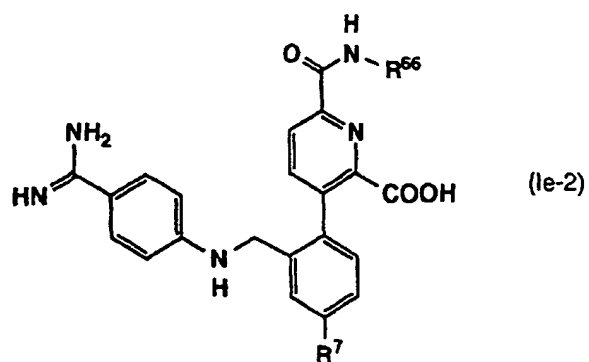
No.	R ⁷	R ⁶⁶	No.	R ⁷	R ⁶⁶
1	H		10	CH ₃	
2	H		11	CH ₃	
3	H		12	CH ₃	
4	H		13	OCH ₃	
5	H		14	OCH ₃	
6	H		15	OCH ₃	
7	CH ₃		16	OCH ₃	
8	CH ₃		17	OCH ₃	
9	CH ₃		18	OCH ₃	

Table 14




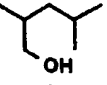

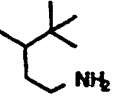
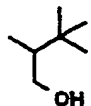
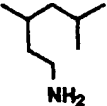
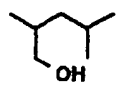

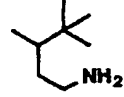

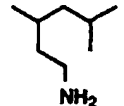
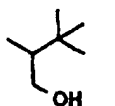

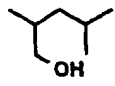

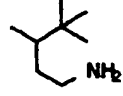
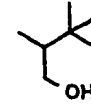
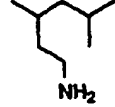
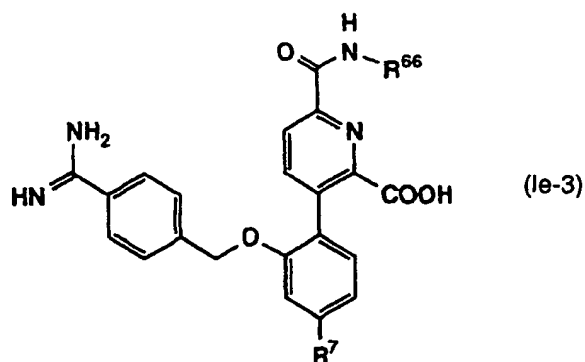
No.	R^7	R^{66}	No.	R^7	R^{66}
1	H		10	CH_3	
2	H		11	CH_3	
3	H		12	CH_3	
4	H		13	OCH_3	
5	H		14	OCH_3	
6	H		15	OCH_3	
7	CH_3		16	OCH_3	
8	CH_3		17	OCH_3	
9	CH_3		18	OCH_3	

Table 15




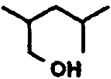

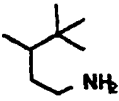
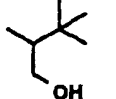
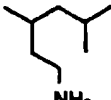
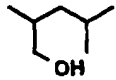

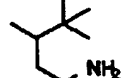

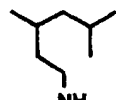


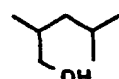

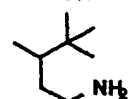
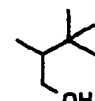
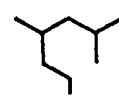
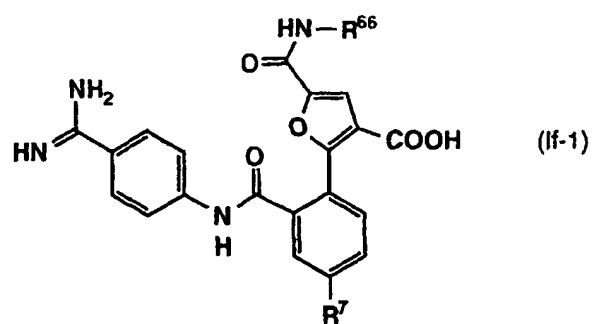
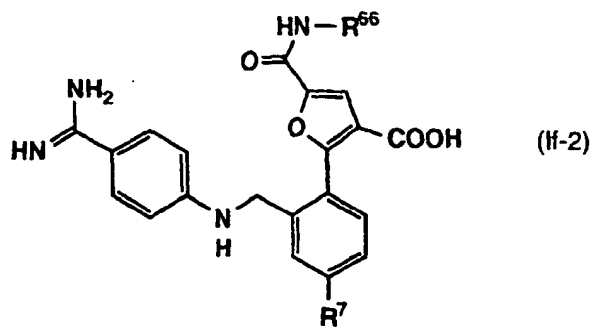
No.	R^7	R^{66}	No.	R^7	R^{66}
1	H		10	CH_3	
2	H		11	CH_3	
3	H		12	CH_3	
4	H		13	OCH_3	
5	H		14	OCH_3	
6	H		15	OCH_3	
7	CH_3		16	OCH_3	
8	CH_3		17	OCH_3	
9	CH_3		18	OCH_3	

Table 16



No.	R ⁷	R ⁶⁶	No.	R ⁷	R ⁶⁶
1	H		10	CH ₃	
2	H		11	CH ₃	
3	H		12	CH ₃	
4	H		13	OCH ₃	
5	H		14	OCH ₃	
6	H		15	OCH ₃	
7	CH ₃		16	OCH ₃	
8	CH ₃		17	OCH ₃	
9	CH ₃		18	OCH ₃	

Table 17



20

25

30

35

40

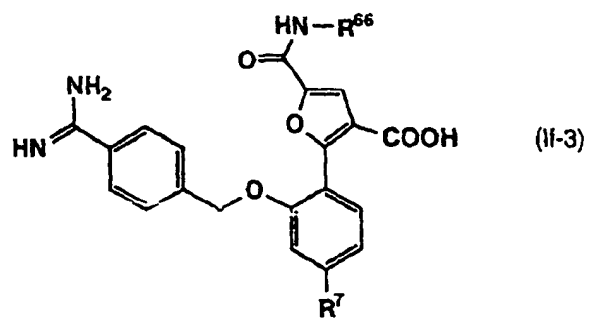
45

50

55

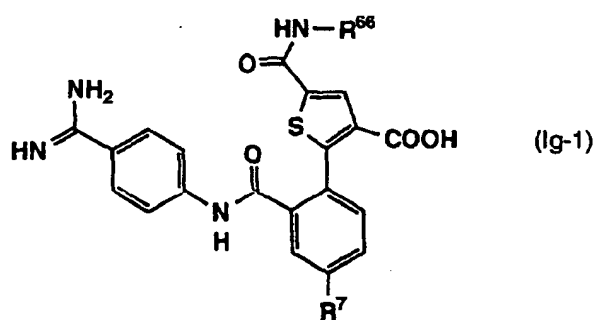
No.	R ⁷	R ⁶⁶	No.	R ⁷	R ⁶⁶
1	H		10	CH ₃	
2	H		11	CH ₃	
3	H		12	CH ₃	
4	H		13	OCH ₃	
5	H		14	OCH ₃	
6	H		15	OCH ₃	
7	CH ₃		16	OCH ₃	
8	CH ₃		17	OCH ₃	
9	CH ₃		18	OCH ₃	

Table 18



No.	R ⁷	R ⁶⁶	No.	R ⁷	R ⁶⁶
1	H		10	CH ₃	
2	H		11	CH ₃	
3	H		12	CH ₃	
4	H		13	OCH ₃	
5	H		14	OCH ₃	
6	H		15	OCH ₃	
7	CH ₃		16	OCH ₃	
8	CH ₃		17	OCH ₃	
9	CH ₃		18	OCH ₃	

Table 19



20

25

30

35

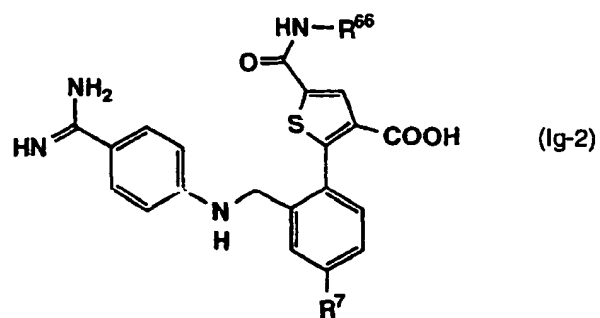
40

45

50

No.	R ⁷	R ⁶⁶	No.	R ⁷	R ⁶⁶
1	H		10	CH ₃	
2	H		11	CH ₃	
3	H		12	CH ₃	
4	H		13	OCH ₃	
5	H		14	OCH ₃	
6	H		15	OCH ₃	
7	CH ₃		16	OCH ₃	
8	CH ₃		17	OCH ₃	
9	CH ₃		18	OCH ₃	

Table 20



20

25

30

35

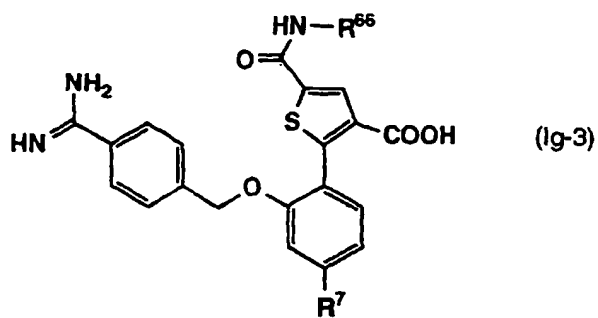
40

45

50

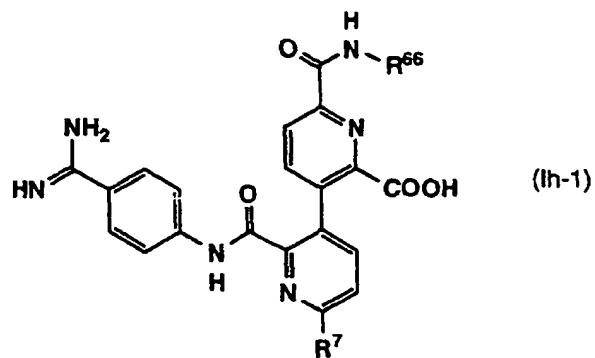
No.	R ⁷	R ⁶⁶	No.	R ⁷	R ⁶⁶
1	H		10	CH ₃	
2	H		11	CH ₃	
3	H		12	CH ₃	
4	H		13	OCH ₃	
5	H		14	OCH ₃	
6	H		15	OCH ₃	
7	CH ₃		16	OCH ₃	
8	CH ₃		17	OCH ₃	
9	CH ₃		18	OCH ₃	

Table 21



No.	R ⁷	R ⁶⁶	No.	R ⁷	R ⁶⁶
1	H		10	CH ₃	
2	H		11	CH ₃	
3	H		12	CH ₃	
4	H		13	OCH ₃	
5	H		14	OCH ₃	
6	H		15	OCH ₃	
7	CH ₃		16	OCH ₃	
8	CH ₃		17	OCH ₃	
9	CH ₃		18	OCH ₃	

Table 22




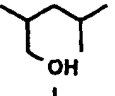

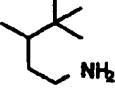
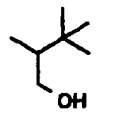
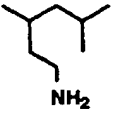
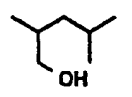

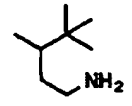

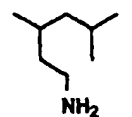
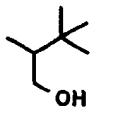

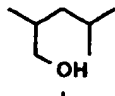

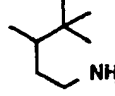
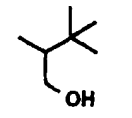
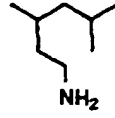
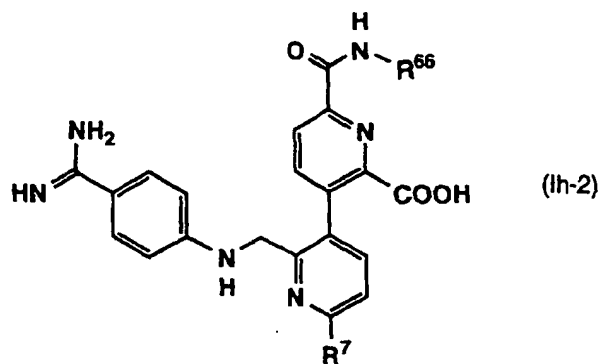
No.	R ⁷	R ⁶⁶	No.	R ⁷	R ⁶⁶
1	H		10	CH ₃	
2	H		11	CH ₃	
3	H		12	CH ₃	
4	H		13	OCH ₃	
5	H		14	OCH ₃	
6	H		15	OCH ₃	
7	CH ₃		16	OCH ₃	
8	CH ₃		17	OCH ₃	
9	CH ₃		18	OCH ₃	

Table 23




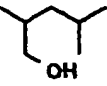

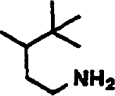
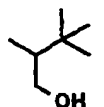
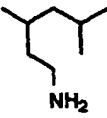
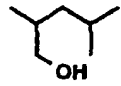

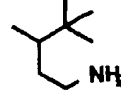

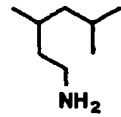
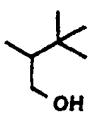

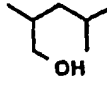

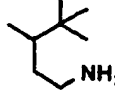
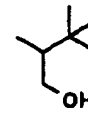
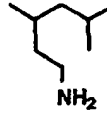
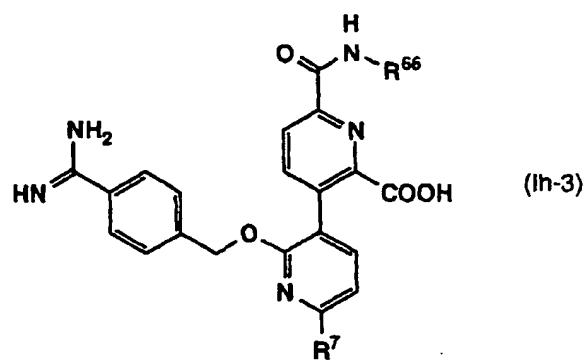
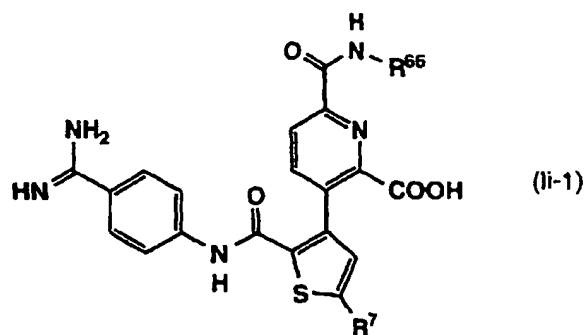
No.	R ⁷	R ⁶⁶	No.	R ⁷	R ⁶⁶
1	H		10	CH ₃	
2	H		11	CH ₃	
3	H		12	CH ₃	
4	H		13	OCH ₃	
5	H		14	OCH ₃	
6	H		15	OCH ₃	
7	CH ₃		16	OCH ₃	
8	CH ₃		17	OCH ₃	
9	CH ₃		18	OCH ₃	

Table 24



No.	R ⁷	R ⁶⁶	No.	R ⁷	R ⁶⁶
1	H		10	CH ₃	
2	H		11	CH ₃	
3	H		12	CH ₃	
4	H		13	OCH ₃	
5	H		14	OCH ₃	
6	H		15	OCH ₃	
7	CH ₃		16	OCH ₃	
8	CH ₃		17	OCH ₃	
9	CH ₃		18	OCH ₃	

Table 25




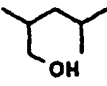

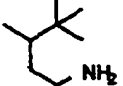
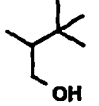
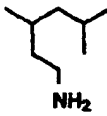
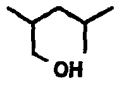

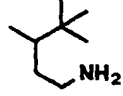

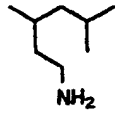
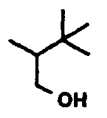

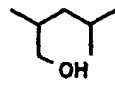

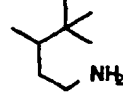
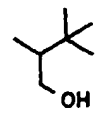
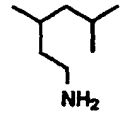
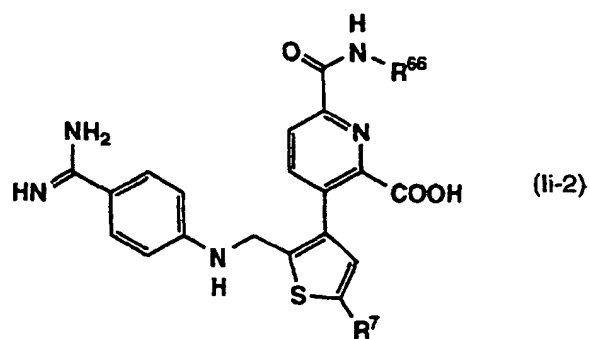
No.	R ⁷	R ⁶⁶	No.	R ⁷	R ⁶⁶
1	H		10	CH ₃	
2	H		11	CH ₃	
3	H		12	CH ₃	
4	H		13	OCH ₃	
5	H		14	OCH ₃	
6	H		15	OCH ₃	
7	CH ₃		16	OCH ₃	
8	CH ₃		17	OCH ₃	
9	CH ₃		18	OCH ₃	

Table 26






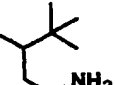
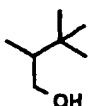
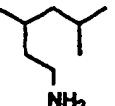
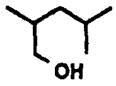

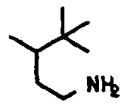

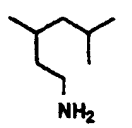
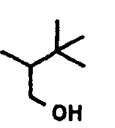

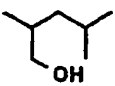

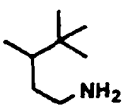
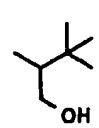
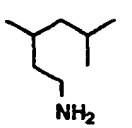
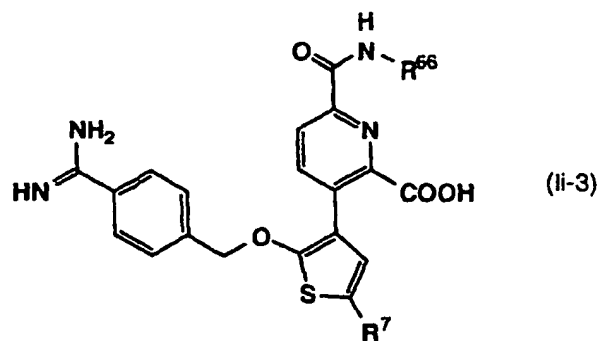

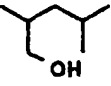

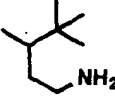
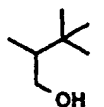
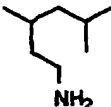
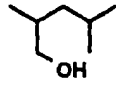

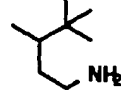

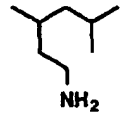
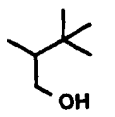

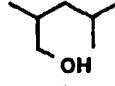

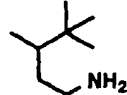
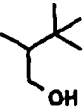
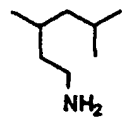
No.	R ⁷	R ⁶⁶	No.	R ⁷	R ⁶⁶
1	H		10	CH ₃	
2	H		11	CH ₃	
3	H		12	CH ₃	
4	H		13	OCH ₃	
5	H		14	OCH ₃	
6	H		15	OCH ₃	
7	CH ₃		16	OCH ₃	
8	CH ₃		17	OCH ₃	
9	CH ₃		18	OCH ₃	

Table 27



No.	R ⁷	R ⁶⁶	No.	R ⁷	R ⁶⁶
1	H		10	CH ₃	
2	H		11	CH ₃	
3	H		12	CH ₃	
4	H		13	OCH ₃	
5	H		14	OCH ₃	
6	H		15	OCH ₃	
7	CH ₃		16	OCH ₃	
8	CH ₃		17	OCH ₃	
9	CH ₃		18	OCH ₃	

Salts

[0043] Non-toxic salts of the present invention include all pharmaceutically acceptable salts.

5 [0044] The compounds of formulae (I) of the present invention may be converted into the corresponding salts. Non-toxic salts and water-soluble salts are preferred. Suitable salts, for example, include: salts of alkali metals (e.g. potassium, sodium), salts of alkaline earth metals (e.g. calcium, magnesium), ammonium salts, salts of pharmaceutically acceptable organic amines (e.g. tetramethylammonium, triethylamine, methylamine, dimethylamine, cyclopentylamine, dicyclohexylamine, benzylamine, phenethylamine, piperidine, monoethanolamine, diethanolamine, tris(hydroxymethyl)amine, lysine, arginine, N-methyl-D-glucamine).

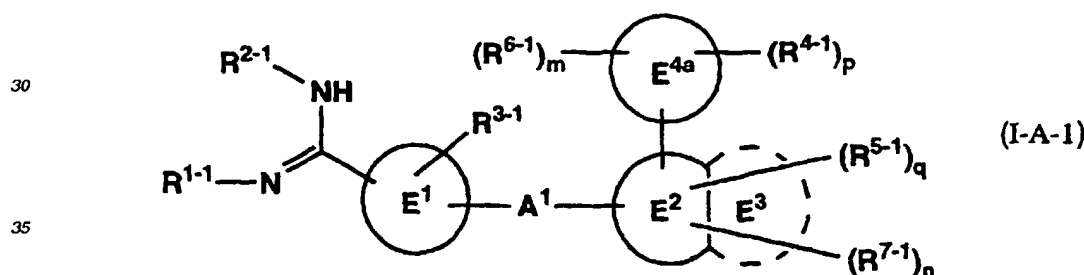
10 [0045] The compounds of formulae (I) may be converted into the corresponding acid addition salts. Non-toxic acid addition salts and water-soluble acid addition salts are preferred. Suitable salts, for example, include: salts of inorganic acids e.g. hydrochloride, hydrobromide, sulfate, phosphate, nitrate; salts of organic acids e.g. acetate, trifluoroacetate, lactate, tartarate, oxalate, fumarate, maleate, citrate, benzoate, methanesulphonate, ethanesulphonate, benzenesulphonate, toluenesulphonate, isethionate, glucuronate, gluconate.

15 [0046] The compounds of formulae (I) and salts thereof may be converted into the corresponding hydrates by conventional manner.

Process for the preparation of the present compound

20 [0047]

(a-1) In the compound of the present invention of the formula (I), the compound in which A is $-NR^{30}CO-$, and R^1 , R^2 and R^3 are not groups including hydroxy, and R^4 and R^5 are groups excepting $CONR^{12}R^{13}$ and are not groups including $-COOH$, $P(O)(OH)_2$ and tetrazol-5-yl, and R^6 and R^7 are not groups including amino and are optionally protected hydroxy, E^4 ring is not pyrrole, furan and thiophene, that is the compound of the formula (I-A-1):



40

wherein R^{1-1} , R^{2-1} and R^{3-1} each independently, is a same meaning as R^1 , R^2 and R^3 , with the proviso that in the case of R^1 , R^2 and R^3 are groups including hydroxy, then the hydroxy represented by corresponding R^{1-1} , R^{2-1} and R^{3-1} is protected hydroxy,

45 R^{4-1} is a same meaning as R^4 excepting $CONR^{12}R^{13}$, with the proviso that in the case of R^4 is groups including $-COOH$, $P(O)(OH)_2$ and tetrazol-5-yl, then $-COOH$, $P(O)(OH)_2$ and tetrazol-5-yl represented by corresponding R^{4-1} are protected $-COOH$, $P(O)(OH)_2$ and tetrazol-5-yl,

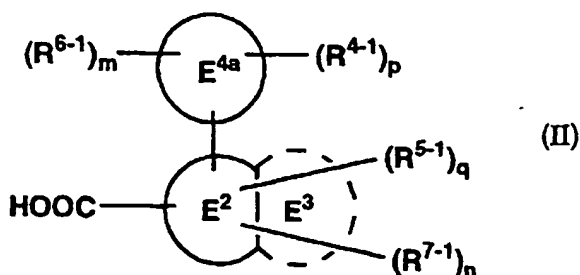
R^{5-1} is a same meaning as R^5 excepting $CONR^{12}R^{13}$, with the proviso that in the case of R^5 is groups including $-COOH$, $P(O)(OH)_2$ and tetrazol-5-yl, then $-COOH$, $P(O)(OH)_2$ and tetrazol-5-yl represented by corresponding R^{5-1} are protected $-COOH$, $P(O)(OH)_2$ and tetrazol-5-yl,

50 R^{6-1} and R^{7-1} are a same meaning as R^6 and R^7 , with the proviso that in the case of R^6 and R^7 are groups including hydroxy and amino, then the hydroxy and amino represented by corresponding R^{6-1} and R^{7-1} are hydroxy or protected hydroxy and protected amino,

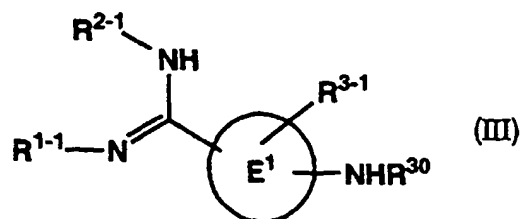
A^1 is $-NR^{30}CO-$,

55 E^{4A} ring is a same meaning as E^4 , with the proviso that it is not pyrrole, furan and thiophene, the other symbols are as hereinbefore defined;

may be prepared by amidation the compound of the formula (II):



15 wherein all the symbols are as hereinbefore defined ;
with the compound of the formula (III):



30 wherein all the symbols are as hereinbefore defined ;
or in the case of the compound in which R^{6-1} and R^{7-1} are the group containing protected hydroxy, continually,
may be prepared by deprotection.

35 The method of amidation is known. It includes the method

- 35
- (1) via an acyl halide,
 - (2) via a mixed acid anhydride,
 - (3) using a condensing agent.

40 These methods are explained as follows.

45 (1) The method via an acyl halide, for example, may be carried out in an organic solvent (e.g. chloroform, methylene chloride, diethyl ether or tetrahydrofuran, ethyl acetate) or without a solvent, using an acyl halide (e.g. oxalyl chloride or thionyl chloride) at -20°C to reflux temperature, and the obtained acyl halide derivative may be reacted with an amine in an organic solvent (e.g. chloroform, methylene chloride, diethyl ether or tetrahydrofuran) in the presence of a tertiary amine (e.g. pyridine, triethyl amine, dimethyl aniline or dimethylaminopyridine) at 0-40°C.

50 (2) The method via a mixed acid anhydride may be carried out, for example, by reacting a carboxylic acid with an acyl halide (e.g. pivaloyl chloride, tosyl chloride, mesyl chloride, ethyl chloroformate or isobutyl chloroformate) in an organic solvent (e.g. chloroform, methylene chloride, diethyl ether or tetrahydrofuran) or without a solvent, in the presence of a tertiary amine (e.g. pyridine, triethylamine, dimethylaniline or dimethylaminopyridine, N-methylmorpholine) at -20°C-40°C, and the obtained mixed acid anhydride derivative may be reacted with a corresponding amine in an organic solvent (e.g. chloroform, methylene chloride, diethyl ether or tetrahydrofuran) at 0-40°C.

55 (3) The method using a condensing agent (e.g. 1, 3-dicyclohexyl carbodiimide (DCC), 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide (EDC) or 2-chloro-1-methylpyridinium iodide, 1, 1'-carbonyldiimidazole (CDI)) may be carried out, for example, by reacting a carboxylic acid with an amine in an organic solvent (e.g. chloroform, methylene chloride, dimethylformamide, diethyl ether, tetrahydrofuran) or without a solvent, optionally in the

presence of a tertiary amine (e.g. pyridine, triethylamine, dimethylaniline or dimethylaminopyridine) using a condensing agent, using 1-hydroxybenzotriazole (HoBt) or without HoBt at 0-40°C.

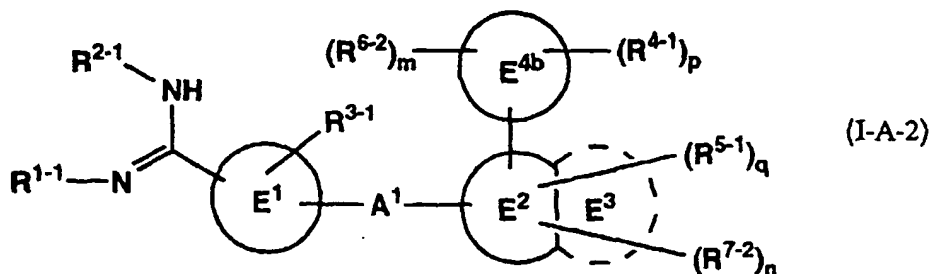
The reaction described in (1), (2) and (3) may be carried out under an inert gas (e.g. argon, nitrogen) to avoid water in order to obtain a preferable result.

The deprotection of hydroxy is known, for example, it includes the method deprotection under acidic conditions or hydrogenolysis.

Deprotection under acidic conditions, for example, may be carried out in a solvent (e.g. methylene chloride, chloroform, dioxane, ethyl acetate, anisole) or without solvent, using an organic acid (e.g. acetic acid, trifluoroacetic acid, methansulfonic acid, trimethylsilyl iodide), or an inorganic acid (e.g. hydrogen chloride) or a mixture thereof (e.g. hydrogen bromide acetic acid) at 0-90 °C.

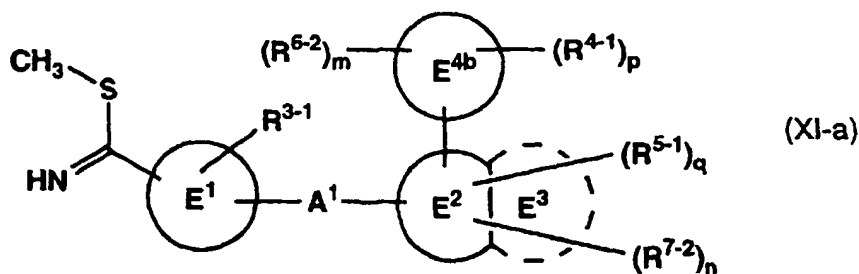
Hydrogenolysis, for example, may be carried out in a solvent (e.g. tetrahydrofuran, dioxane, diethyl ether, ethyl acetate, methanol, ethanol), in the presence of a catalyst (e.g. palladium on carbon, palladium, palladium hydroxide, palladium acetate, palladium black, platinum black, nickel or Raney-nickel), at ordinary or elevated pressure of hydrogen gas at 0-80 °C.

(a-2) In the compound of the present invention of the formula (I), the compound in which A is $-NR^{30}CO-$, and R^1 , R^2 and R^3 are not groups including hydroxy, and R^4 and R^5 are groups excepting $CONR^{12}R^{13}$ and are not groups including $-COOH$, $P(O)(OH)_2$ and tetrazol-5-yl, and R^6 and R^7 are not groups including hydroxy and amino, E^4 ring is pyrrole, furan or thiophene, that is the compound of the formula (I-A-2):



wherein E^{4b} is pyrrole, furan or thiophene, R^{6-2} and R^{7-2} are a same meaning as R^6 and R^7 , with the proviso that in the case of R^6 and R^7 are groups including hydroxy and amino, then the hydroxy and amino represented by corresponding R^{6-2} and R^{7-2} are protected hydroxy and protected amino, the other symbols are as hereinbefore defined;

may be prepared by subjecting to condensation reaction, the compound of the formula (XI-a):



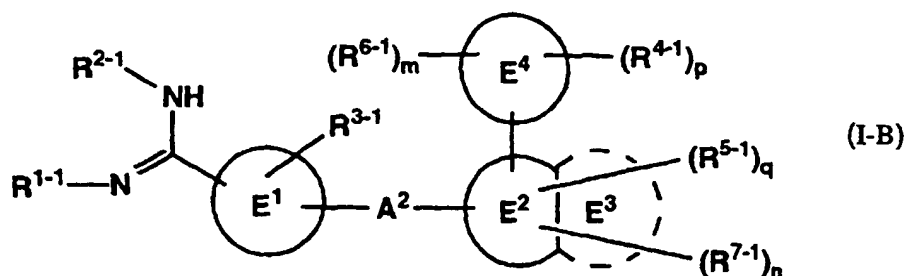
wherein all the symbols are as hereinbefore defined ;
with the compound of the formula (IX):



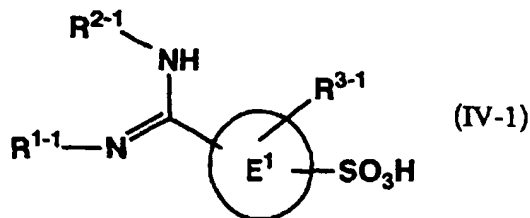
wherein R^1 is as hereinbefore defined.

The condensation reaction is known, for example, it may be carried out by reacting with the compound of the formula (IX) or salt thereof in organic solvent (e.g. methanol, ethanol, acetonitrile, methylene chloride, diethyl ether, tetrahydrofuran, toluene, dimethylformamide) without a solvent, optionally in the presence of a base (e.g. triethylamine, sodium hydride, sodium methoxide, sodium ethoxide) at 0 °C to reflux temperature.

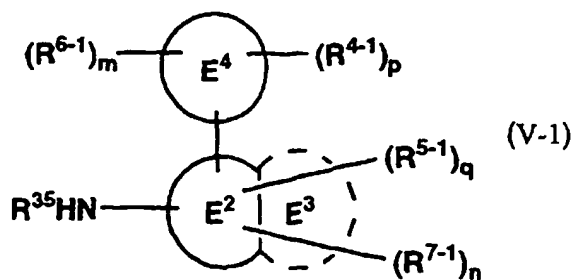
(b) In the compound of the present invention of the formula (I), the compound in which A is $-\text{SO}_2\text{NR}^{34}-$ or $-\text{NR}^{35}\text{SO}_2-$, and R^1 , R^2 and R^3 are not groups including hydroxy, and R^4 and R^5 are groups excepting $\text{CONR}^{12}\text{R}^{13}$ and are not groups including $-\text{COOH}$, $\text{P}(\text{O})(\text{OH})_2$ and tetrazol-5-yl, and R^6 and R^7 are not groups including amino and optionally protected hydroxy, that is the compound of the formula (I-B):



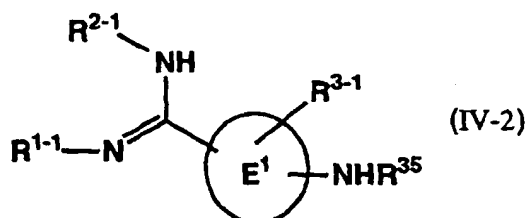
wherein A^2 is $-\text{SO}_2\text{NR}^{34}-$ or $-\text{NR}^{35}\text{SO}_2-$, the other symbols are as hereinbefore defined; may be prepared by reacting the compound of the formula (IV-1):



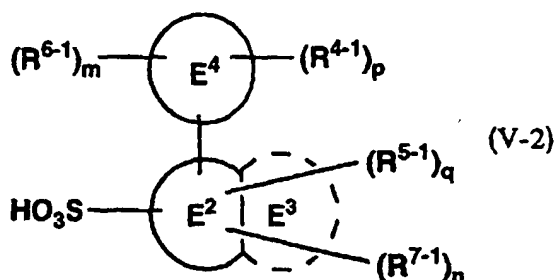
wherein all the symbols are as hereinbefore defined; with the compound of the formula (V-1):



wherein all the symbols are as hereinbefore defined; or by reacting the compound of the formula (IV-2):



wherein all the symbols are as hereinbefore defined;
with the compound of the formula (V-2):

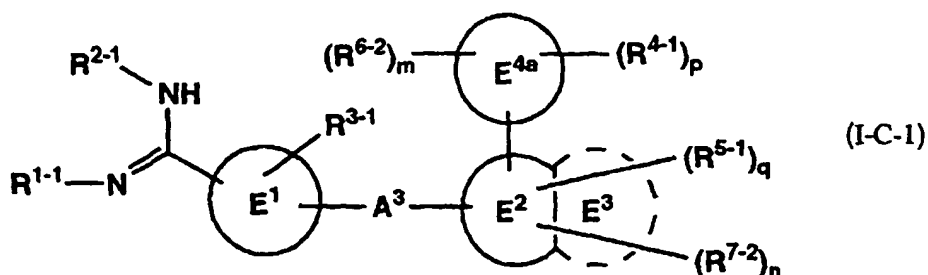


wherein all the symbols are as hereinbefore defined;
or in the case of the compound in which R^{6-1} and R^{7-1} are the group containing protected hydroxy, continually, may be prepared by deprotection.

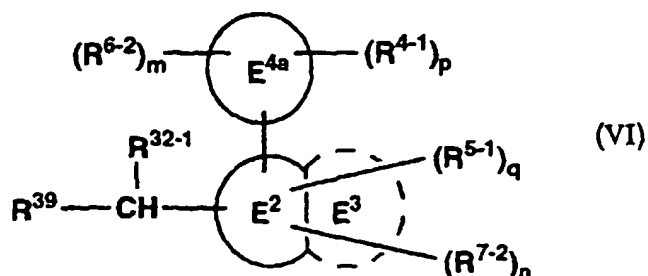
The above reaction is known, for example, may be carried out by reacting sulfonic acid and acyl halide (e.g. oxalyl chloride or thionyl chloride) in an organic solvent (e.g. chloroform, methylene chloride, diethyl ether, tetrahydrofuran, ethyl acetate) or without a solvent at -20°C to reflux temperature, and the obtained acyl halide derivative may be reacted with an amine in an organic solvent (e.g. chloroform, methylene chloride, diethyl ether or tetrahydrofuran) in the presence of a tertiary amine (e.g. pyridine, triethyl amine, dimethyl aniline or dimethylaminopyridine) at $0-40^{\circ}\text{C}$.

The deprotection reaction is known, for example, may be carried out as method hereinbefore defined.

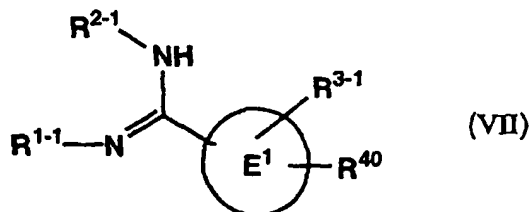
(c-1) In the compound of the present invention of the formula (I), the compound in which A is $-\text{O}-\text{CH}_2-$, $-\text{S}-\text{CH}_2-$, $-\text{NR}^{31}\text{CHR}^{32-1}-$, and R^1 , R^2 and R^3 are not groups including hydroxy, and R^4 and R^5 are groups excepting $\text{CONR}^{12}\text{R}^{13}$ and are not groups including $-\text{COOH}$, $\text{P}(\text{O})(\text{OH})_2$ and tetrazol-5-yl, and R^6 and R^7 are not groups including hydroxy and amino, E^4 ring is not pyrrole, furan and thiophene, that is the compound of the formula (I-C-1):



wherein A^3 is $-O-CH_2-$, $-S-CH_2-$ or $-NR^{31}CHR^{32-1}$, in which R^{32-1} is hydrogen, cyano, $COOR^{36-1}$, in which R^{36-1} is C1-4 alkyl; or $CONR^{37-1}R^{38-1}$, in which R^{37-1} and R^{38-1} each independently, is hydrogen, C1-4 alkyl, but both are not hydrogen at the same time; the other symbols are as hereinbefore defined; may be prepared by alkylation the compound of the formula (VI):



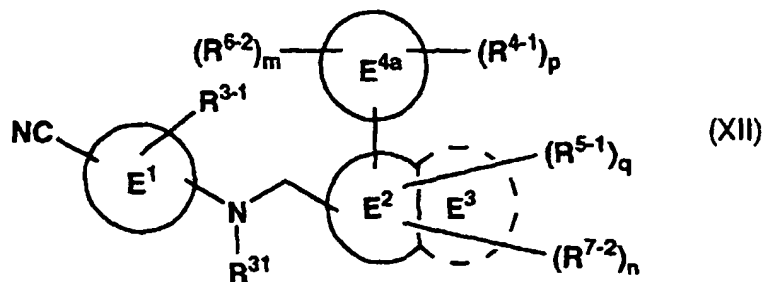
wherein R^{39} is halogen atom, methansulfonyloxy or p-toluenesulfonyloxy, the other symbols are as hereinbefore defined; with the compound of the formula (VII):



wherein R^{40} is $-OH$, $-SH$ or $-NHR^{31}$, the other symbols are as hereinbefore defined.

The above alkylation is known, for example, may be carried out in an inert organic solvent (e.g. tetrahydrofuran (THF), diethyl ether, methylene chloride, chloroform, carbon tetrachloride, pentane, hexane, benzene, toluene, dimethylformamide (DMF), dimethylsulfoxide (DMSO), hexamethylphosphoric triamide (HMPA)), in the presence of an base (e.g. sodium hydride, potassium carbonate, triethylamine, pyridine, sodium iodide, cesium carbonate) at 0-80 °C.

In the case of the compound in which A^3 or $-NR^{31}CH_2-$, it may be also prepared by subjecting the compound of the formula (XII):

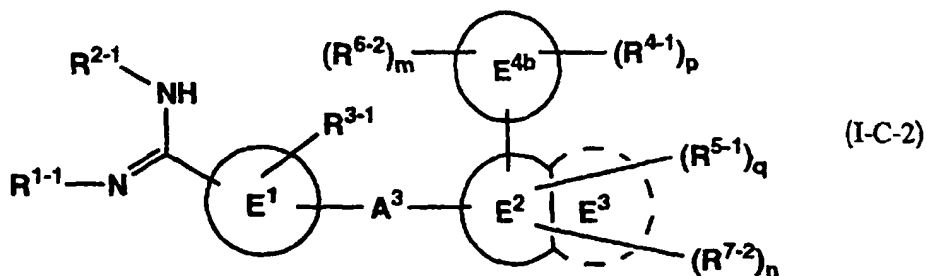


wherein all the symbols are as hereinbefore defined; to pinner method.

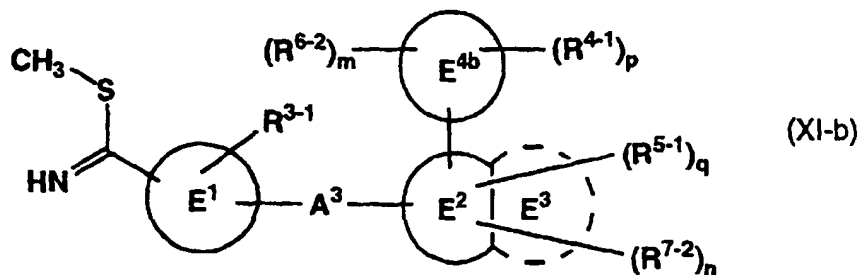
The pinner method is known, for example, it may be carried out in an organic solvent (e.g. ethanol, methylene

chloride) using hydrochloride at 0-50 °C, continually, in an organic solvent (e.g. methanol, ethanol) using ammonium gas at 0-50 °C.

(c-2) In the compound of the present invention of the formula (I), the compound in which A is -O-CH₂-, -S-CH₂- or -NR³¹CHR³²⁻¹-, and R¹, R² and R³ are not groups including hydroxy, and R⁴ and R⁵ are groups excepting CONR¹²R¹³ and are not groups including -COOH, P(O)(OH)₂ and tetrazol-5-yl, and R⁶ and R⁷ are not groups including hydroxy and amino, E⁴ ring is pyrrole, furan or thiophene, that is the compound of the formula (I-C-2):



wherein A³ is -O-CH₂-, -S-CH₂- or -NR³¹CHR³²⁻¹-, the other symbols are as hereinbefore defined; may be prepared by subjecting to condensation reaction, the compound of the formula (XI-b):



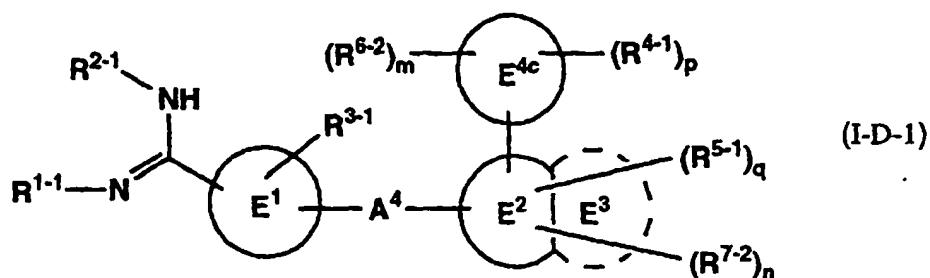
wherein all the symbols are as hereinbefore defined; with the compound of the formula (IX):



wherein R¹ is as hereinbefore defined.

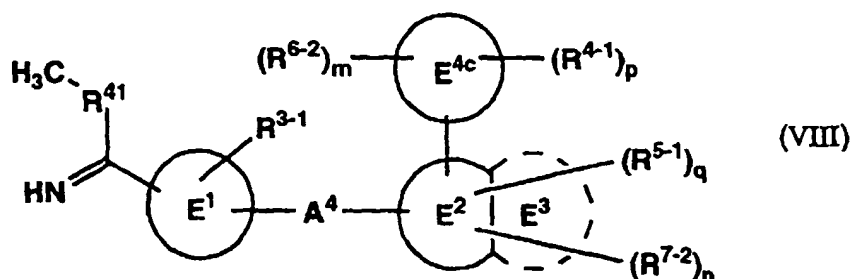
The condensation reaction is known, for example, it may be carried out as method hereinbefore defined.

(d-1) In the compound of the present invention of the formula (I), the compound in which A is vinylene, ethynylene, -CH₂-O-, -CH₂-NR³³-, -CH₂-S-, and R³ are not groups including hydroxy, and R⁴ and R⁵ are groups excepting CONR¹²R¹³ and are not groups including -COOH, P(O)(OH)₂ and tetrazol-5-yl, and R⁶ and R⁷ are not groups including hydroxy and amino, when A is vinylene or ethynylene, then E⁴ ring is not pyrrole, furan and thiophene, that is the compound of the formula (I-D-1):



15 wherein A^4 is vinylene, ethynylene, $-\text{CH}_2-\text{O}-$, $-\text{CH}_2-\text{NR}^{33}-$, $-\text{CH}_2-\text{S}-$, E^{4c} ring is a same meaning as E^4 ring, with the proviso that it is not pyrrole, furan and thiophene, when A is vinylene or ethynylene, the other symbols are as hereinbefore defined;

may be prepared by subjecting to condensation reaction, the compound of the formula (VIII):



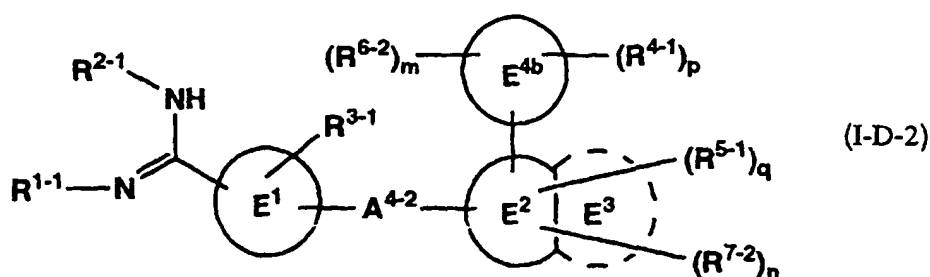
35 wherein R^{41} is $-\text{O}-$ or $-\text{S}-$, and the other symbols are as hereinbefore defined; with the compound of the formula (IX):



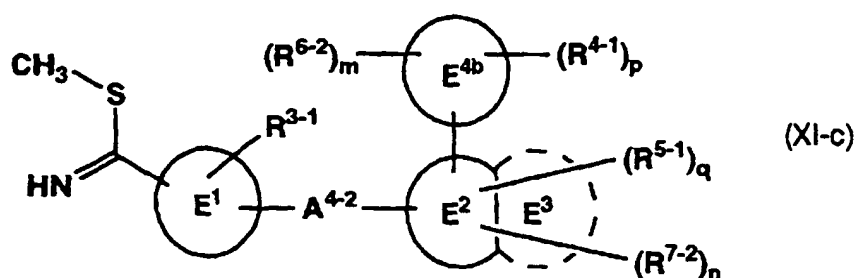
wherein R^1 is as hereinbefore defined.

The above reaction is known, for example, the compound of the formula (VIII) may be carried out by reacting with the compound of the formula (IX) or salts thereof in an organic solvent (e.g. methanol, ethanol, acetonitrile, methylene chloride, diethyl ether, tetrahydrofuran, toluene, dimethylformamide) or without a solvent, optionally in the presence of a base (e.g. triethylamine, sodium hydride, sodium methoxide, sodium ethoxide) at 0°C to reflux temperature.

45 (d-2) In the compound of the present invention of the formula (I), the compound in which A is vinylene, ethynylene, and R^3 are not groups including hydroxy, and R^4 and R^5 are groups excepting $\text{CONR}^{12}\text{R}^{13}$ and are not groups including $-\text{COOH}$, $\text{P}(\text{O})(\text{OH})_2$ and tetrazol-5-yl, and R^6 and R^7 are not groups including hydroxy and amino, E^4 ring is pyrrole, furan or thiophene, that is the compound of the formula (I-D-2):



15 wherein A^{4-2} is vinylene, ethynylene, and the other symbols are as hereinbefore defined; may be prepared by subjecting to condensation reaction, the compound of the formula (XI-c):



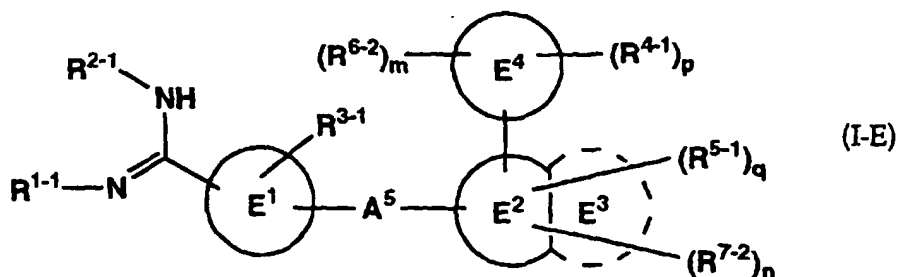
30 wherein all the symbols are as hereinbefore defined; with the compound of the formula (IX):



wherein R^1 is as hereinbefore defined.

The condensation reaction is known, for example, it may be carried out as method hereinbefore defined.

40 (e) In the compound of the present invention of the formula (I), the compound in which A is ethylene, and R^1 , R^2 and R^3 are not groups including hydroxy, and R^4 and R^5 are groups excepting $CONR^{12}R^{13}$ and are not groups including $-COOH$, $P(O)(OH)_2$ and tetrazol-5-yl, and R^6 and R^7 are not groups including hydroxy and amino, that is the compound of the formula (I-E):

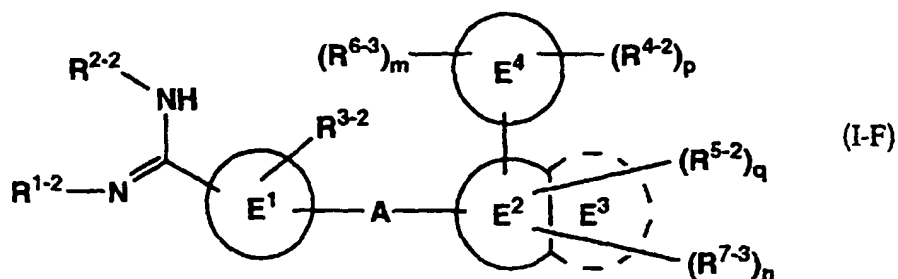


wherein A^5 is ethylene, and the other symbols are as hereinbefore defined; may be prepared by subjecting to reduction the compound in which A^4 is vinylene or ethynylene in the compound of the formula (I-D-1), or the com-

pound of the formula (I-D-2).

The above reduction reaction is known, for example, in an organic solvent (e.g. tetrahydrofuran, dioxane, diethyl ether, ethyl acetate, methanol, ethanol), using a catalyst (e.g. palladium on carbon, palladium, palladium hydroxide, palladium acetate, palladium black, platinum black, nickel or Raney-nickel), at ordinary or elevated pressure of hydrogen gas at 0-80 °C.

(f) In the compound of the present invention of the formula (I), R^4 and R^5 are groups excepting $\text{CONR}^{12}\text{R}^{13}$, R^1 , R^2 and R^3 are groups including hydroxy, or R^4 and R^5 are groups including $-\text{COOH}$, $\text{P}(\text{O})(\text{OH})_2$ and tetrazol-5-yl, or R^6 and R^7 are groups including hydroxy and amino, that is the compound of the formula (I-F):



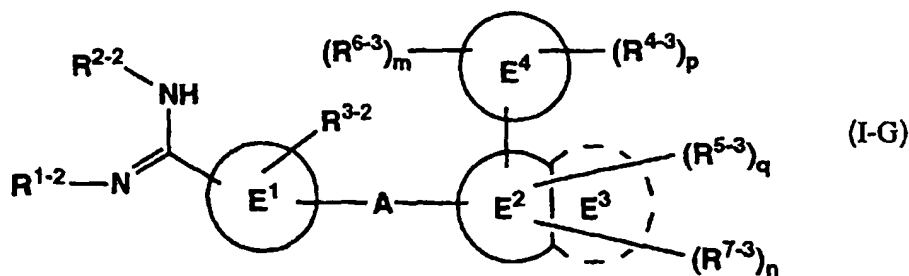
wherein R^{1-2} , R^{2-2} , R^{3-2} , R^{6-3} and R^{7-3} each is the same meaning as R^1 , R^2 , R^3 , R^6 and R^7 , R^{4-2} and R^{5-2} each is the same meaning as R^4 and R^5 excepting $\text{CONR}^{12}\text{R}^{13}$, with the proviso that at least one of R^{1-2} , R^{2-2} , R^{3-2} , R^{4-2} , R^{5-2} , R^{6-3} and R^{7-3} is hydroxy, $-\text{COOH}$, amino, $\text{P}(\text{O})(\text{OH})_2$, tetrazol-5-yl, or a group including them, the other symbols are as hereinbefore defined; may be prepared by deprotection under an alkaline condition, deprotection under an acidic conditions and / or hydrogenolysis, the compound of the formula (I-A-1), (I-A-2), (I-B), (I-C-1), (I-C-2), (I-D-1), (I-D-2) or (I-E).

Deprotection under an alkaline condition is known, for example, may be carried out in an organic solvent (e.g. methanol, tetrahydrofuran, dioxane), using an alkali metal hydroxide (e.g. sodium hydroxide, potassium hydroxide, lithium hydroxide), an alkaline earth metal hydroxide (e.g. calcium hydroxide) or a carbonate (e.g. sodium carbonate, potassium carbonate), or an aqueous solution thereof or mixture thereof at 0-40°C.

Deprotection under acidic conditions, for example, may be carried out in a solvent (e.g. methylene chloride, chloroform, dioxane, ethyl acetate, anisole) or without a solvent, using an organic acid (e.g. acetic acid, trifluoroacetic acid, methanesulfonic acid, trimethylsilyl iodide), or an inorganic acid (e.g. hydrogen chloride) or a mixture thereof (e.g. hydrogen bromide acetic acid) at 0-90°C.

Hydrogenolysis, for example, may be carried out in a solvent (e.g. tetrahydrofuran, dioxane, diethyl ether, methanol, ethanol), in the presence of a catalyst (e.g. palladium on carbon, palladium, palladium hydroxide, palladium acetate, palladium black, platinum black, nickel or Raney-nickel), at ordinary or elevated pressure of hydrogen gas at 0-80°C.

(g) In the compound of the present invention of the formula (I), R^4 and R^5 are $\text{CONR}^{12}\text{R}^{13}$, that is the compound of the formula (I-G):



wherein R^{4-3} and R^{5-3} each independently, is $CONR^{12}R^{13}$, and R^{1-2} , R^{2-2} , R^{3-2} , R^{6-3} and R^{7-3} each is the same meaning as R^1 , R^2 , R^3 , R^6 and R^7 , with the proviso that at least one of R^{1-2} , R^{2-2} , R^{3-2} , R^{6-3} and R^{7-3} is hydroxy, -COOH, amino or a group including them, the other symbols are as hereinbefore defined;
 may be prepared by amidation the compound in which at least one of R^4 and R^5 is -COOH or a group including it
 in the compound of the formula (I-F), with the compound of the formula (X):



wherein all the symbols are as hereinbefore defined.

[0048] Amidation is known, for example, it may be carried out by the same method as hereinbefore described.

[0049] As will be apparent to those skilled in the art, t-butyl or benzyl may be used as protecting groups for carboxyl, and t-butyl, benzyl, t-butyldimethylsilyl, trimethylsilyl may be used as protecting groups for hydroxy, but other groups which may be removed easily and selectively are also preferred. For example, the groups described in T.W. Greene, Protective Groups in Organic Synthesis, Wiley, New York, 1991, may be used.

[0050] Benzyloxycarbonyl, t-butoxycarbonyl may be used as protecting groups for amino, but other groups which may be removed easily and selectively are also preferred.

[0051] t-Butyl or benzyl may be used as protecting groups for hydroxylamine, but other groups which may be removed easily and selectively are also preferred. For example, $-C(CH_3)_2-OCH_3$ may be used.

[0052] The desired compound of the present invention may be easily prepared using these protecting groups.

[0053] The compound of the formula (II), (III), (IV-1), (IV-2), (V-1), (V-2), (VI), (VII), (VIII), (IX), (X), (XI-a), (XI-b), (XI-c) and (XII) are known per se or may be prepared by known methods, or methods in the Examples.

[0054] For example, the compound of the formula (II), (V-1), (V-2), (VI), (VIII), (XI), and (XII) may be prepared by using a reaction depicted in following schemes.

[0055] Symbols in each schemes mean as follows, the other symbols are as hereinbefore defined.

L : OTf, halogen atom,

Tf : trifluoromethansulfonyl,

M : $-B(OH)_2$, $-Sn(C1-4 \text{ alkyl})_3$,

R^{42} : a general protecting groups of amine,

R^{43} : a general protecting groups of hydroxy,

Tf_2O : trifluoromethansulfonic acid anhydrous,

$HC(SMe)_3$: tris(methylthio)methane,

NBS : N-bromosuccinimide,

TMSCN : trimethylsilylcyanide,

HCl_{aq} : an aqueous solution of hydrochloric acid,

MsCl : methanesulfonyl chloride,

TsCl : p-toluenesulfonyl chloride,

A^{4-1} : $-CH_2-O-$, $-CH_2-NR^{33}-$, $-CH_2-S-$,

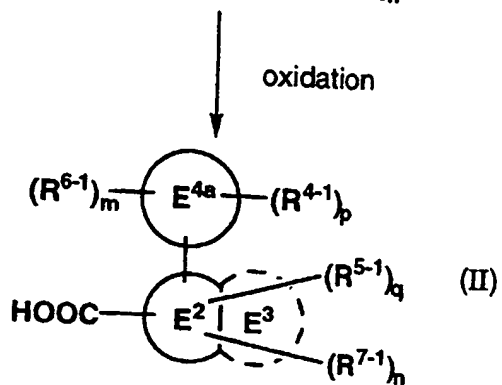
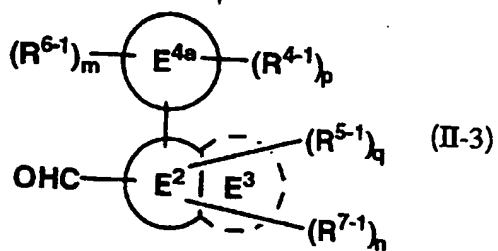
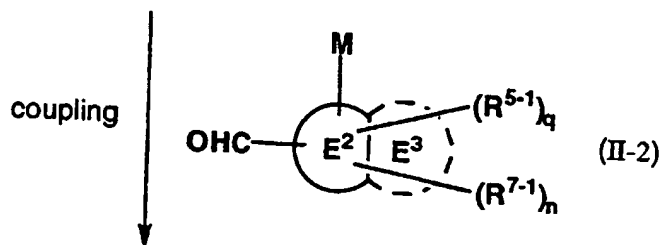
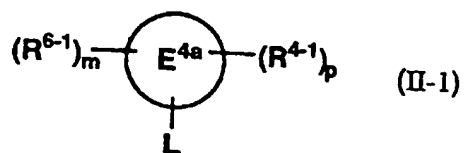
A^6 : $-NR^{30}CO-$, $-O-CH_2-$, $-S-CH_2-$, $-NR^{31}CHR^{32-1}$ -, vinylene, ethynylene,

NaSH : sodium bisulfate,

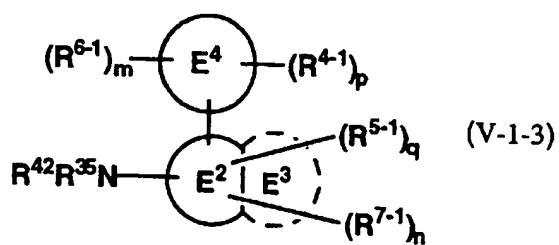
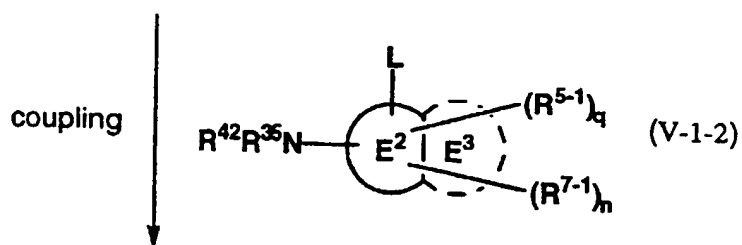
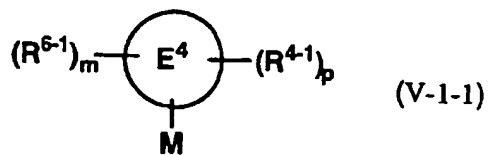
Mel : methyl iodide,

MeOH : methanol.

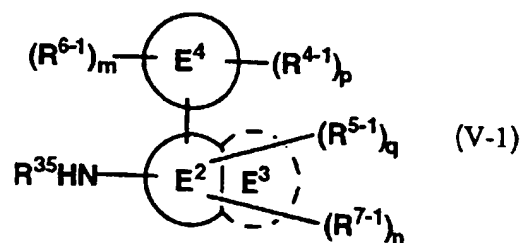
Scheme 1



Scheme 2



deprotection



Scheme 3

5

10

15

20

25

30

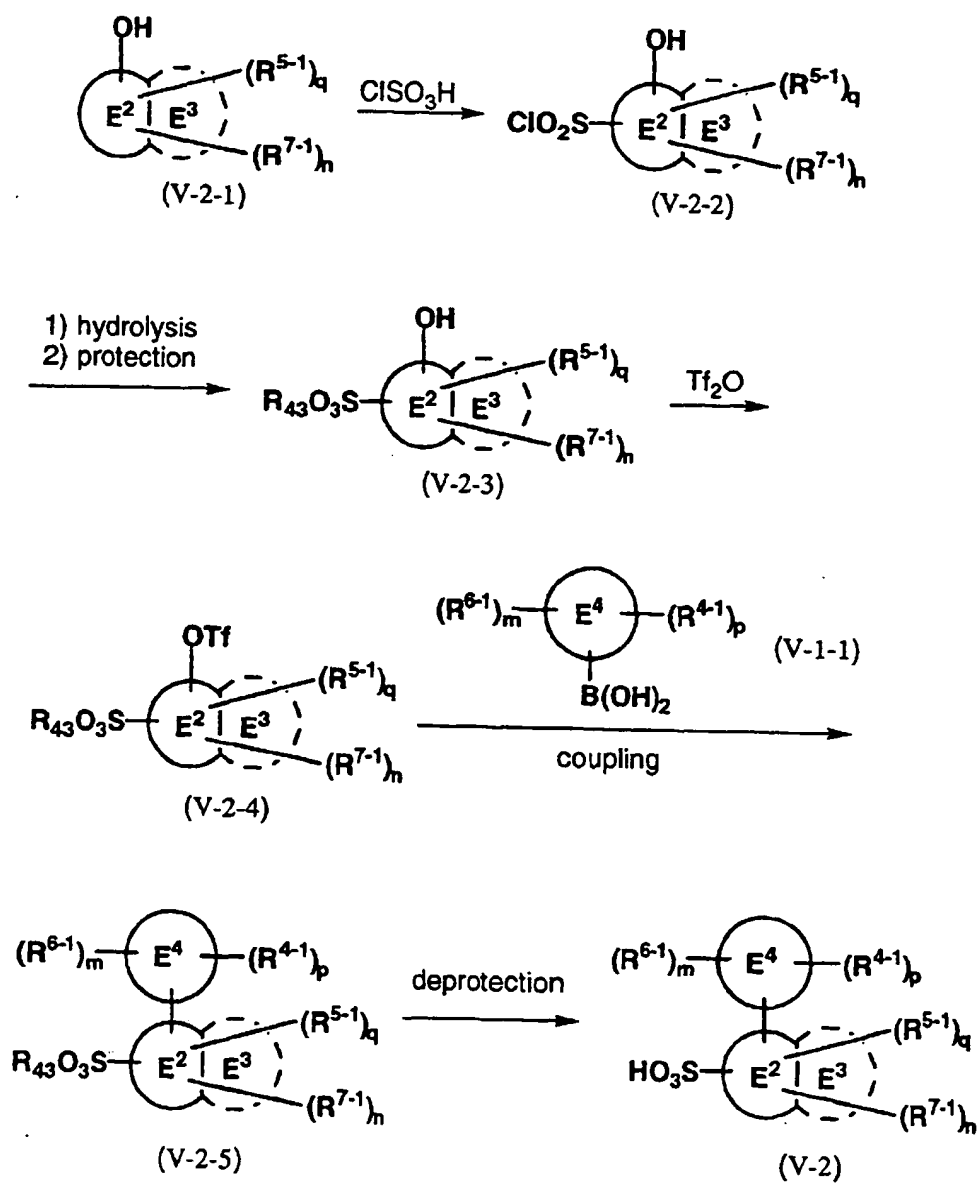
35

40

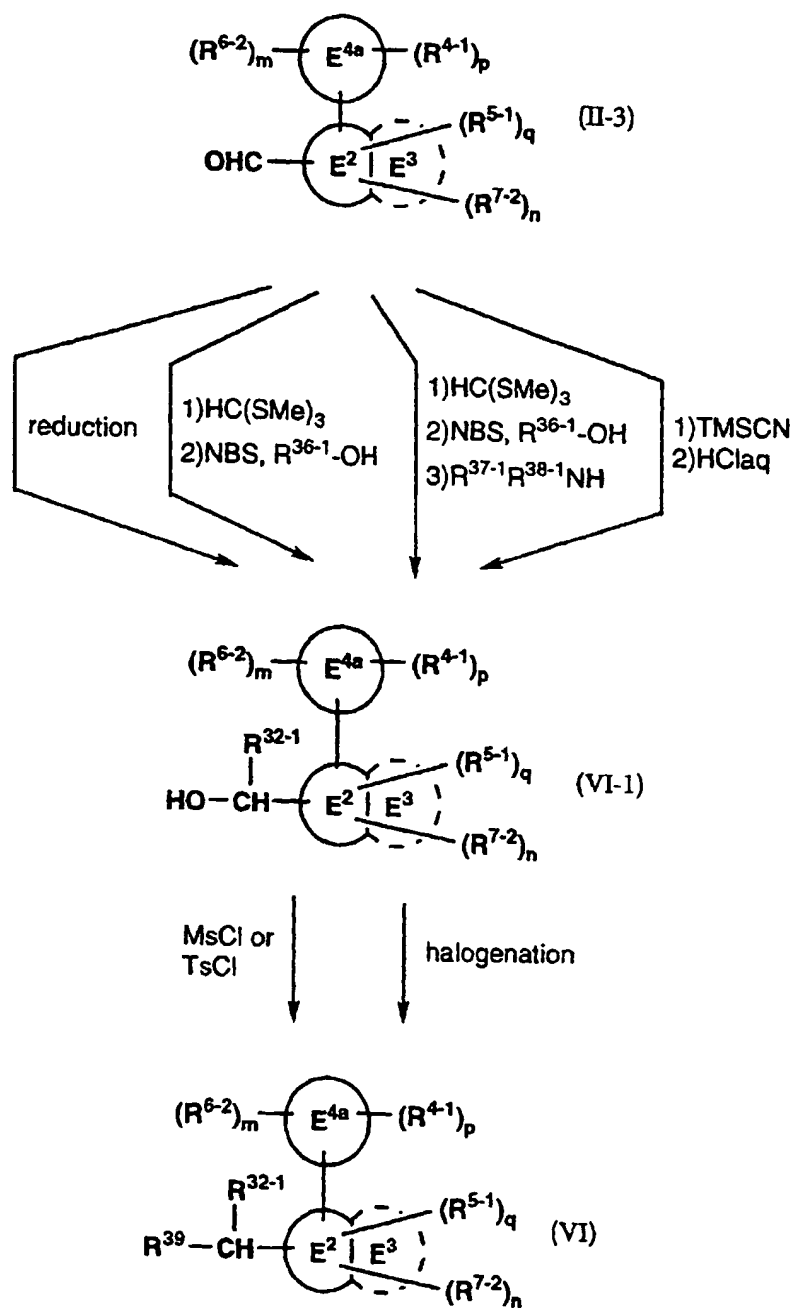
45

50

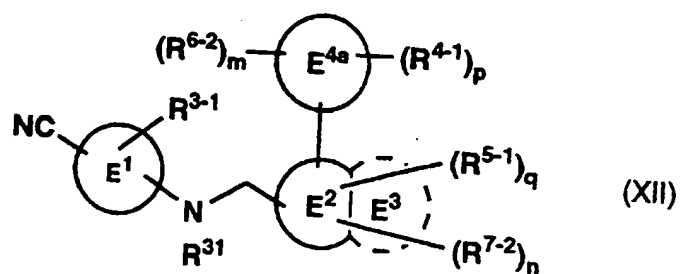
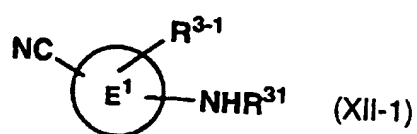
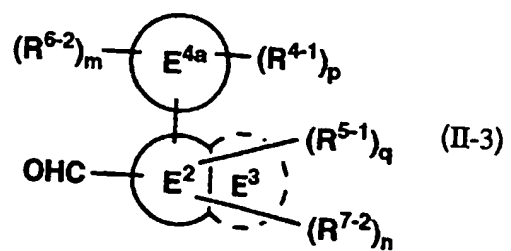
55



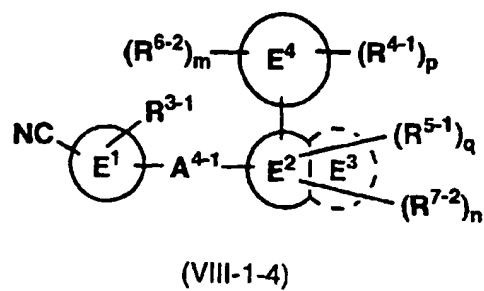
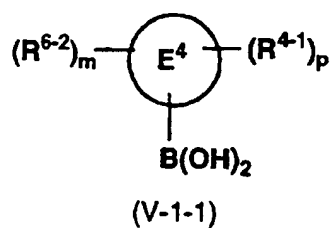
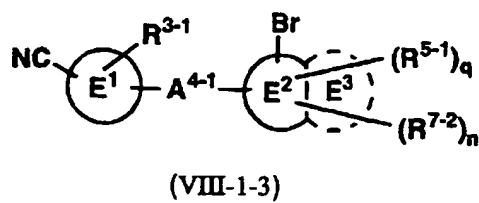
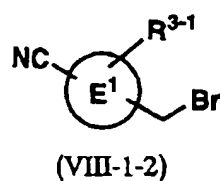
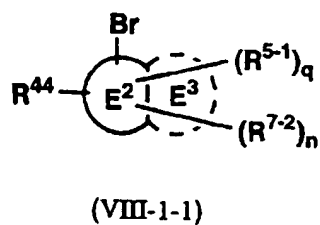
Scheme 4-1



Scheme 4-2



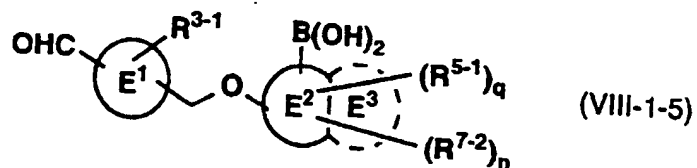
Scheme 5-1



Scheme 5-2

5

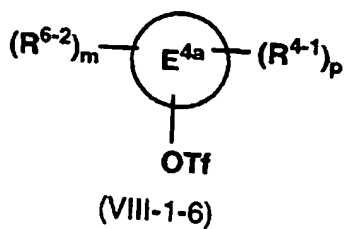
10



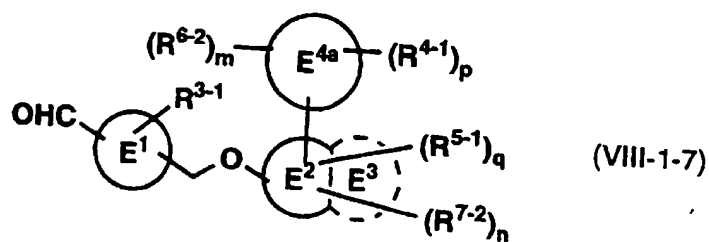
15

20

25



30

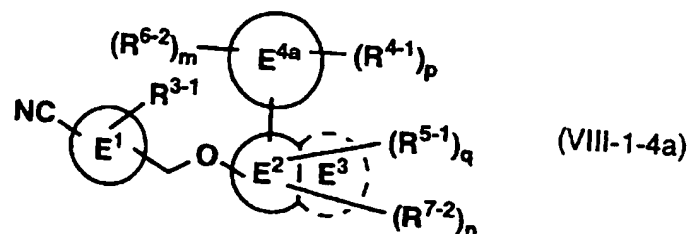


35

40

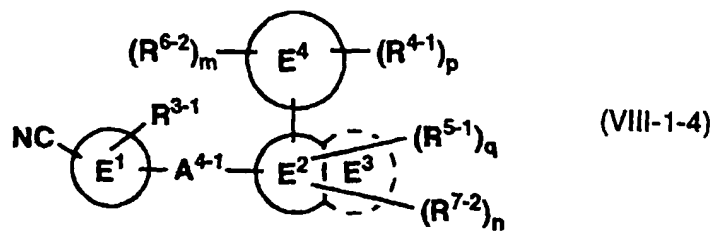
HCl. NH₂OH

45



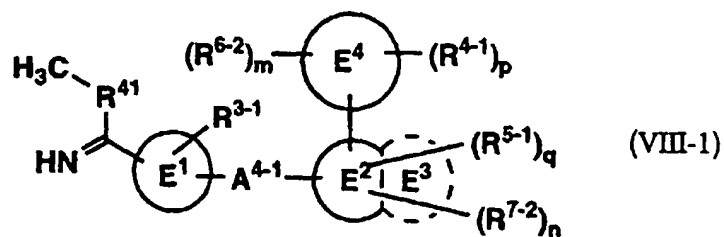
50

55

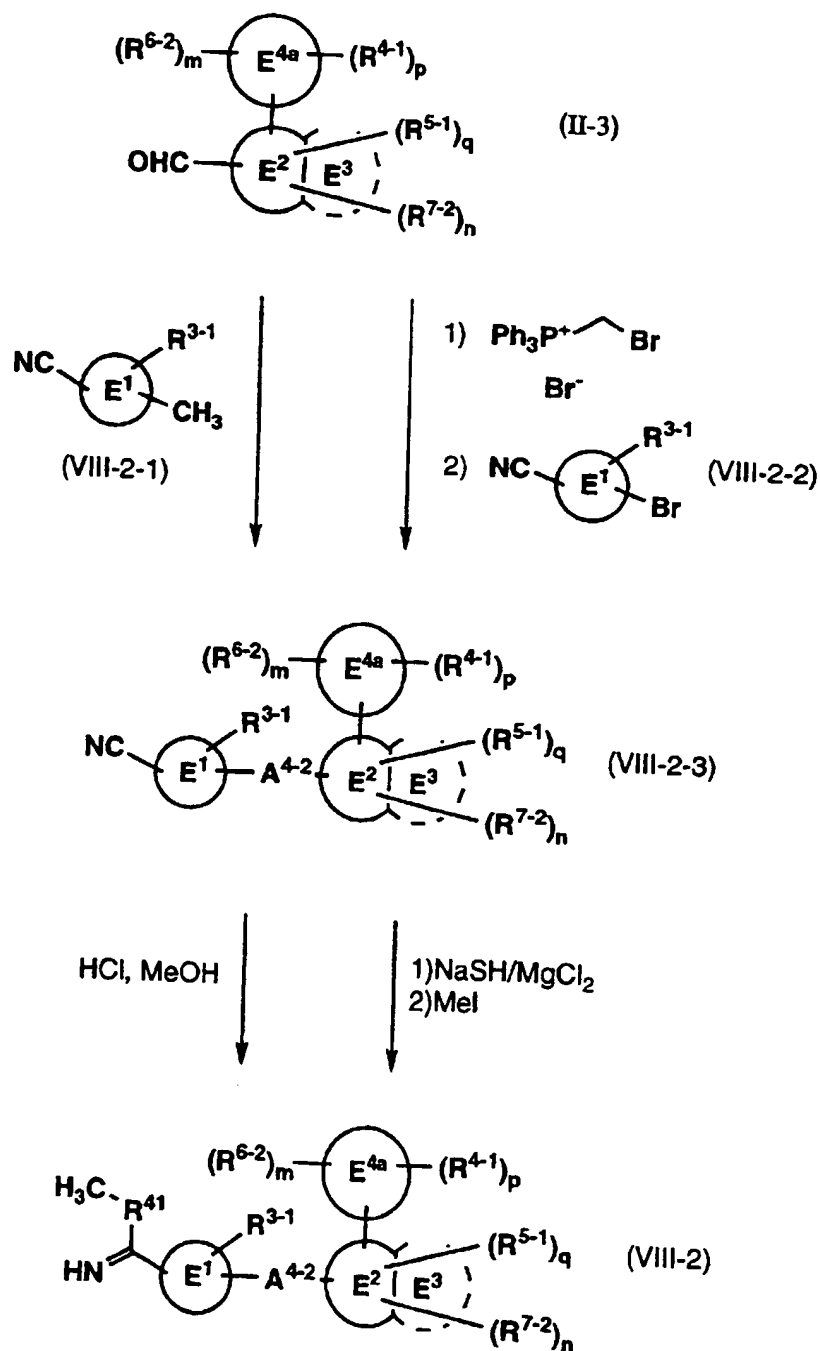
Scheme 5-3

1) NaSH/MgCl₂
2) MeI

HCl, MeOH



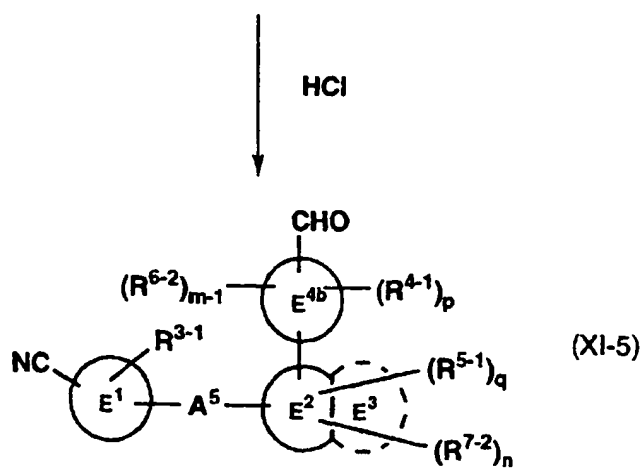
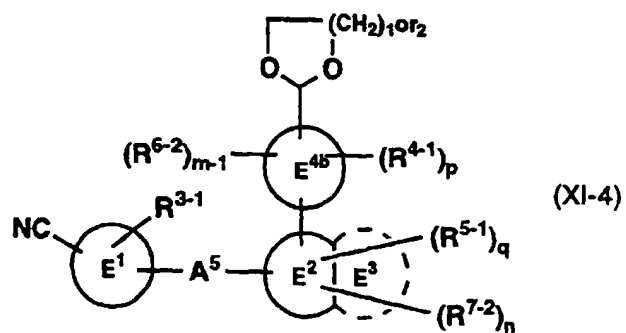
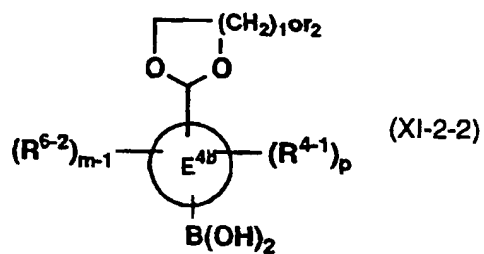
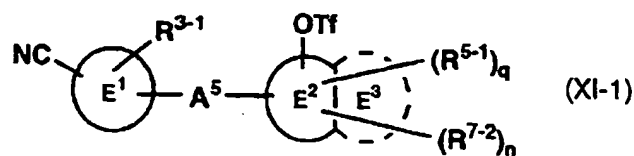
Scheme 6



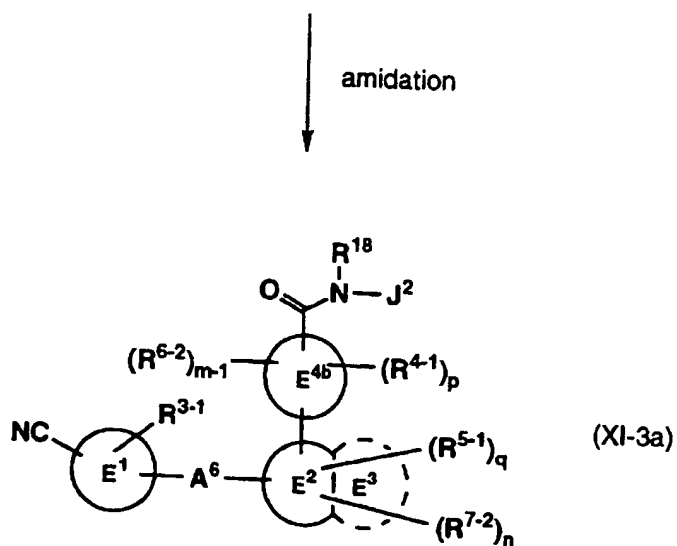
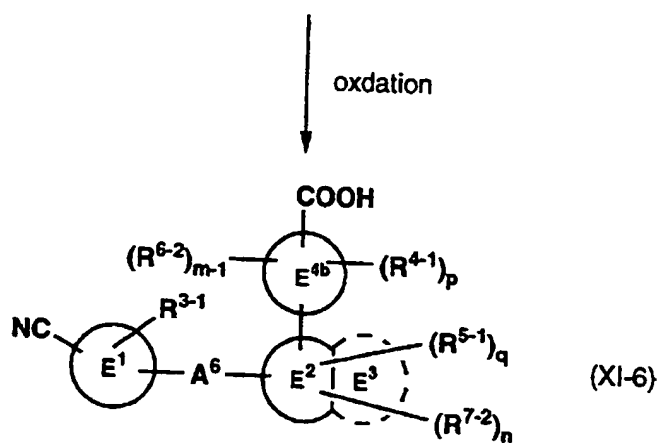
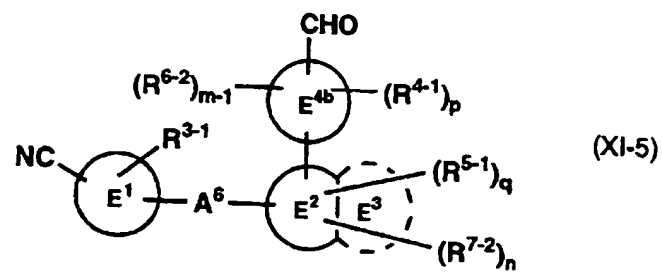
10



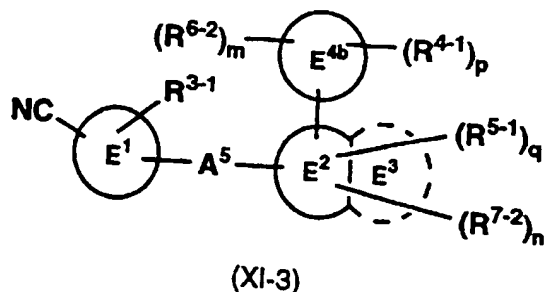
Scheme 7-2



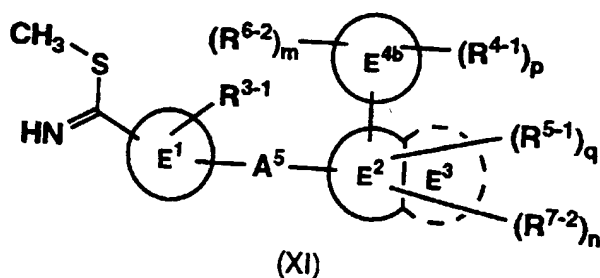
Scheme 7-3



Scheme 7-4



1) NaSH/MgCl₂
2) MeI



[0056] The starting materials in each scheme are known per se or may be prepared by known methods.

[0057] The reaction in each scheme are carried out by known methods.

[0058] The other starting materials and reagents in the present invention are known per se or may be prepared by known methods.

Pharmacological Activities

(1) FVIIa inhibitory activity

[0059] 10 μ l of the compound of the present invention in 10 % DMSO were added to 65 μ l of the buffer solution including FVIIa (ADI#407, final 10 nM), tissue factor (ADI#4500, final 10 nM) and calcium chloride. The mixture was incubated for 10 minutes at 37 °C, then 25 μ l of 2 mM H-D-Ile-Pro-Arg-pNA (Chromogenix S-2288) was added (total volume 100 μ l). The absorbance was measured at 405 nm at regular time intervals, and an initial velocity was calculated. The control value was measured with 10% of DMSO. Inhibitory activity was expressed as a 50% inhibition of control (IC50).

[0060] The final concentration of calcium chloride and S-2288 were 2 mM and 0.5 mM respectively. The buffer solution consisted of 50 mM tris-hydrochloric acid buffer (pH 7.5) containing 0.2 % PEG6000 and 150 mM sodium chloride.

[0061] These results are shown in Table 28.

Table 28

Compound	IC50 (μ M)
Example 19(47)	0.012
Example 46	0.013

5

10 (2) Anticoagulant effect on the prothrombin time (PT) and the activated partial thromboplastin time (APTT)

[0062] PT is assayed by addition of tissue factor and indicates the coagulant activity of the extrinsic pathway, and APTT is assayed by addition of negative charged substances and indicates the coagulant activity of the intrinsic pathway.

15 [0063] The assay method was as follows.

[0064] Purified human plasma (verify reference plasma, organon technica) and the compound of the present invention in 10% DMSO solution were mixed at the rate of 9 : 1.

(a) PT determination

20

[0065] An automatic coagulation determination device (Sysmex CA5000) was used for the measurement of blood coagulation time, using the plasma described above and thromboplastin C (Dade).

[0066] The control value was determined by adding solvent without the compound of the present invention. The concentration of the compound of the present invention at which the coagulation time prolonged two time of the control (PTCT2), was calculated.

25

(b) APTT determination

[0067] An automatic coagulation determination device (Sysmex CA5000) was used for the measurement of blood coagulation time, using the plasma described above, datefy APTT (Dade) and 20 mM calcium chloride.

30

[0068] The control value was determined by adding solvent without the compound of the present invention. The concentration of the compound of the present invention at which the coagulation time prolonged two time of the control (APTTCT2), was calculated, and an extension rate (%) of APTT on PTCT2 were estimated.

[0069] An extension rate of APTT on PTCT2 of the compound of the present invention was not effective.

35

Industrial Applicability

Toxicity

40 [0070] The toxicity of the compounds of the present invention is very low and therefore the compounds may be considered safe for pharmaceutical use.

Utility

45 [0071] The formula (I) of amidino derivatives, their non-toxic salts and hydrates have an inhibitory activity for a blood coagulation factor VIIa and are useful for treatment and / or prevention of several angiopathologic diseases due to the hypercoagulability, such as disseminated intravascular coagulation, coronary thrombosis (e.g. acute myocardial infarction, unstable angina), cerebral infarction, cerebral embolism, transient ischemic attack, diseases caused by cerebrovascular disorders, pulmonary vascular diseases (e.g. pulmonary infarction, pulmonary embolism), deep venous thrombosis, peripheral arterial obstruction, thrombosis after artificial vascular transplantation and artificial valve transplantation, post-operative thrombosis, reobstruction and restenosis after coronary artery bypass operation, reobstruction and restenosis after PTCA (percutaneous transluminal coronary angioplasty) or PTCR (percutaneous transluminal coronary recanalization), thrombosis by extracorporeal circulation and procoagulative diseases such as glomerulonephritis.

50

Application for Pharmaceuticals

[0072] For the purpose above described, the compounds of formulae (I) of the present invention, non-toxic salts,

acid addition salts or hydrates thereof may be normally administered systemically or locally, usually by oral or parenteral administration.

[0073] The doses to be administered are determined depending upon, for example, age, body weight, symptom, the desired therapeutic effect, the route of administration, and the duration of the treatment. In the human adult, the doses per person are generally from 1 mg to 1000 mg, by oral administration, up to several times per day, and from 0.1 mg to 100 mg, by parenteral administration (preferably intravenous administration), up to several times per day, or continuous administration from 1 to 24 hours per day from vein.

[0074] As mentioned above, the doses to be used depend upon various conditions. Therefore, there are cases in which doses lower than or greater than the ranges specified above may be used.

[0075] The compounds of the present invention may be administered in the form of, for example, solid forms for oral administration, liquid forms for oral administration, injections, liniments or suppositories for parenteral administration.

[0076] Solid forms for oral administration include compressed tablets, pills, capsules, dispersible powders, and granules. Capsules include hard capsules and soft capsules.

[0077] In such solid forms, one or more of the active compound(s) may be admixed with vehicles (such as lactose, mannitol, glucose, microcrystalline cellulose, starch), binders (such as hydroxypropyl cellulose, polyvinylpyrrolidone or magnesium metasilicate aluminate), disintegrants (such as cellulose calcium glycolate), lubricants (such as magnesium stearate), stabilizing agents, and solution adjuvants (such as glutamic acid or aspartic acid) and prepared according to methods well known in normal pharmaceutical practice. The solid forms may, if desired, be coated with coating agents (such as sugar, gelatin, hydroxypropyl cellulose or hydroxypropylmethyl cellulose phthalate), or be coated with two or more films. And further, coating may include containment within capsules of absorbable materials such as gelatin.

[0078] Liquid forms for oral administration include pharmaceutically acceptable solutions, suspensions and emulsions, syrups and elixirs. In such forms, one or more of the active compound(s) may be dissolved, suspended or emulsified into diluent(s) commonly used in the art (such as purified water, ethanol or a mixture thereof). Besides such liquid forms may also comprise some additives, such as wetting agents, suspending agents, emulsifying agents, sweetening agents, flavoring agents, aroma, preservative or buffering agent.

[0079] Injections for parenteral administration include sterile aqueous, suspensions, emulsions and solid forms which are dissolved or suspended into solvent(s) for injection immediately before use. In injections, one or more of the active compound(s) may be dissolved, suspended or emulsified into solvent(s). The solvents may include distilled water for injection, physiological salt solution, vegetable oil, propylene glycol, polyethylene glycol, alcohol, e.g. ethanol, or a mixture thereof.

[0080] Injections may comprise some additives, such as stabilizing agents, solution adjuvants (such as glutamic acid, aspartic acid or POLYSORBATE80 (registered trade mark)), suspending agents, emulsifying agents, soothing agent, buffering agents, preservative. They may be sterilized at a final step, or may be prepared and compensated according to sterile methods. They may also be manufactured in the form of sterile solid forms which may be dissolved in sterile water or some other sterile diluent(s) for injection immediately before use.

[0081] Other forms for parenteral administration include liquids for external use, ointments and endermic liniments, inhalations, sprays, suppositories and pessaries for vaginal administration which comprise one or more of the active compound(s) and may be prepared by methods known per se. Sprays may comprise additional substances other than diluents, such as stabilizing agents (such as sodium sulfate), isotonic buffers (such as sodium chloride, sodium citrate or citric acid). For preparation of such sprays, for example, the method described in the United States Patent No. 2,868,691 or 3,095,355 may be used.

Best Mode for Carrying Out the Invention

[0082] The following Reference Examples and Examples illustrate the present invention, but do not limit the present invention.

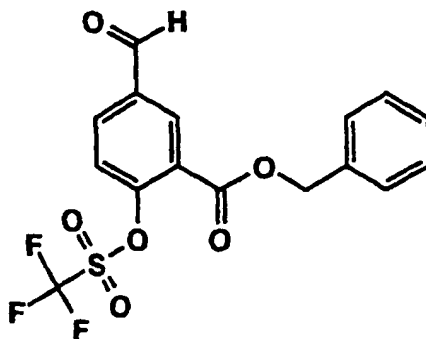
[0083] The solvents in the parentheses show the developing or eluting solvents and the ratios of the solvents used are by volume in chromatographic separations or TLC.

[0084] The solvents in the parentheses in NMR show the solvents used in measurement.

Reference Example 1

Benzyl 2-trifluoromethylsulfonyloxy-5-formylbenzoate

5 [0085]



20

[0086] Potassium bicarbonate (3.3 g) and benzyl bromide (3.9 ml), successively, were added to a solution of 2-hydroxy-5-formylbenzoic acid (5 g) in dimethylformamide (80 ml) under an atmosphere of argon at room temperature. The mixture was stirred for 14 hours at room temperature. The reaction mixture was poured into water (150 ml). The solution was extracted with ethyl acetate. The extract was washed with a saturated aqueous solution of sodium chloride, dried over anhydrous magnesium sulfate and concentrated. To a solution of the residue (5.9 g) in methylene chloride (25 ml), pyridine (9.3 ml) and trifluoromethanesulfonic acid anhydrous (7.7 ml), successively, were added under an atmosphere of argon at 0 °C. The mixture was stirred for 30 minutes. The reaction mixture was poured into water (60 ml). The solution was extracted with ethyl acetate (150 ml). The extract was washed with a saturated aqueous solution of sodium chloride, dried over anhydrous magnesium sulfate and concentrated. The residue was purified by column chromatography on silica gel (hexane : ethyl acetate = 5 : 1) to give the present compound (6.23 g) having the following physical data.

35 TLC : R_f 0.33 (Hexane : Ethyl acetate = 5 : 1) ;
 NMR (CDCl₃) : δ 10.1 (1H, s), 8.57 (1H, d, J = 2.2 Hz), 8.16 (1H, dd, J = 2.2, 8.4 Hz), 7.52-7.38 (6H, m), 5.45 (2H, s).

40

45

50

55

Reference Example 2

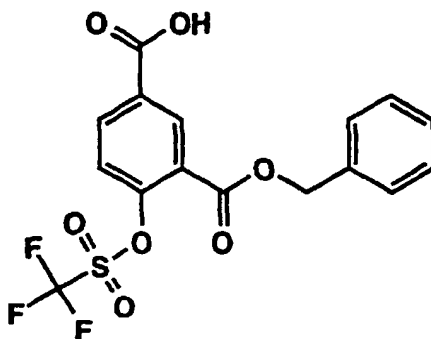
3-benzyloxycarbonyl-4-trifluoromethylsulfonyloxybenzoic acid

5 [0087]

10

15

20



[0088] To the mixed solution of the compound prepared in Reference Example 1 (1.86 g) in t-butanol - acetonitrile - water (27 ml ; 6 : 1 : 2), 2-methyl -2-butene (2.3 ml), sodium dihydrogenphosphate (690 mg) and sodium chloride (1.9 g), successively, were added. The mixture was stirred for 20 minutes at room temperature. The reaction mixture was poured into ice-water. The solution was extracted with ethyl acetate (60 ml, 2 times). The extract was washed with a saturated aqueous solution of sodium chloride, dried over anhydrous magnesium sulfate and concentrated. The residue (1.94 g) was used to the next reaction without being purified.

30 TLC : Rf 0.23 (Chloroform : Methanol : Water = 9 : 1 : 0.1).

Reference Example 3

Benzyl 2-trifluoromethylsulfonyloxy-5-((2,2-dimethylpropyl)carbamoyl) benzoate

35

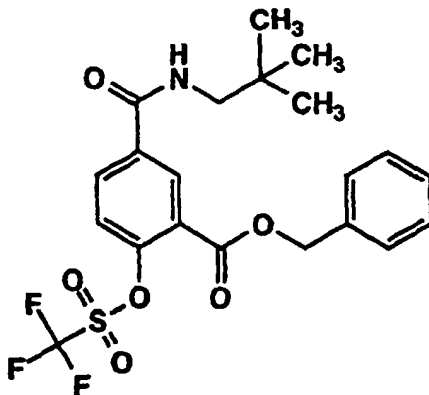
[0089]

40

45

50

55



[0090] Oxalyl chloride (0.21 ml) and dimethylformamide (1 drop) were added to a solution of the compound (808 mg) prepared in Reference Example 2 in methylene chloride (8 ml) under an atmosphere of argon at 0 °C. The mixture

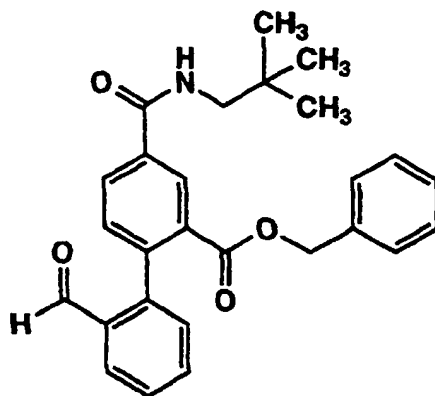
was stirred for 3 minutes at 0 °C, and stirred for 1 hour at room temperature. The reaction mixture was concentrated. The residue was distilled off an azeotropic mixture with toluene (5 ml, 2 times). The residue was dissolved into methylene chloride (8 ml), and cooled to 0 °C. Triethylamine (0.5 ml) and 2,2-dimethylpropylamine (0.24 ml) were added to the solution. The mixture was stirred for 5 minutes at 0 °C, stirred for 10 minutes at room temperature. The reaction mixture was poured into ice-water (30 ml). The solution was extracted with ethyl acetate (30 ml, 2 times). The extract was washed with a saturated aqueous solution of sodium chloride, dried over anhydrous magnesium sulfate and concentrated. The residue was purified by column chromatography on silica gel (hexane : ethyl acetate = 5 : 1) to give the present compound (857 mg) having the following physical data.

NMR (CDCl₃) : δ 8.39 (1H, d, J = 2.6 Hz), 8.08 (1H, dd, J = 2.6, 8.4 Hz), 7.50-7.37 (6H, m), 6.16 (1H, brs), 5.44 (2H, s), 3.28 (2H, d, J = 6.4 Hz), 0.98 (9H, s).

Reference Example 4

Benzyl 2'-formyl-4-((2,2-dimethylpropyl)carbamoyl)-2-biphenylcarboxylate

[0091]



[0092] 2-formylphenylboric acid (269 mg), tripotassium phosphate (569 mg) and tetrakis(triphenylphosphine)palladium (0) (62 mg), successively, were added to a solution of the compound prepared in Reference Example 3 (847 mg) in dimethylformamide (7 ml). The mixture was stirred for 30 minutes at 100 °C. The reaction mixture was poured into ice-water (30 ml). The solution was extracted with ethyl acetate (30 ml, 2 times). The extract was washed with a saturated aqueous solution of sodium chloride, dried over anhydrous magnesium sulfate and concentrated. The residue was purified by column chromatography on silica gel (hexane : ethyl acetate = 3 : 1) to give the present compound (770 mg) having the following physical data.

TLC : R_f 0.27 (Hexane : Ethyl acetate = 3 : 1) ;

NMR (CDCl₃) : δ 9.76 (1H, s), 8.41 (1H, d, J = 1.8 Hz), 8.02 (1H, dd, J = 1.8, 8.0 Hz), 7.87 (1H, dd, J = 1.6, 7.8 Hz), 7.57-7.25 (6H, m), 7.20-7.16 (1H, m), 7.10-7.05 (2H, m), 6.27 (1H, brs), 5.04 (2H, s), 3.32 (2H, d, J = 6.2 Hz), 1.01 (9H, s).

Reference Example 5

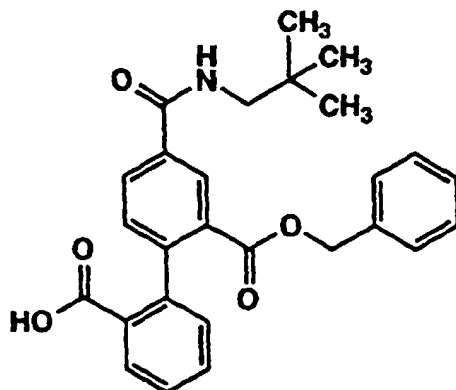
2'-benzyloxycarbonyl-4'-((2,2-dimethylpropyl)carbamoyl)-2-biphenylcarboxylic acid

5 [0093]

10

15

20



25 [0094] The title compound having the following physical data was obtained by the same procedure as a series of reaction of Reference Example 2, using a compound prepared in Reference Example 4.

TLC : Rf 0.38 (Chloroform : Methanol : Water = 9 : 1 : 0.1).

Example 1

30

Benzyl 2'-((4-amidinophenyl)carbamoyl)-4'-((2,2-dimethylpropyl)carbamoyl)-2-biphenylcarboxylic acid

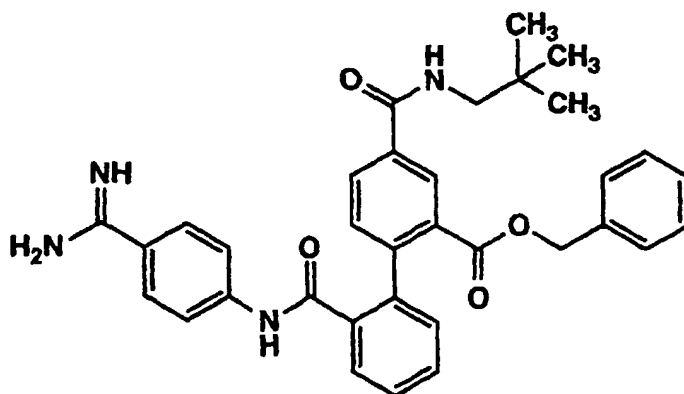
[0095]

35

40

45

50



55 [0096] Dicyclohexylcarbodiimide (513 mg), pyridine (7 ml) and 4-amidinoaniline (345 mg), successively, were added to a solution of the compound prepared in Reference Example 5 (740 mg) in dimethylformamide (7 ml). The mixture was stirred over night. The reaction mixture was filtered, and the filtrate was concentrated. The residue was purified by column chromatography on silica gel (Chloroform : Methanol : Water = 9 : 1 : 0.1 → 8 : 2 : 0.1) to give the present compound (835 mg) having the following physical data.

EP 1 078 917 A1

TLC : Rf 0.38 (Chloroform : Methanol : Water = 8 : 2 : 0.1) ;

NMR (CD₃OD) : δ 8.32 (1H, d, J = 2.0 Hz), 7.97 (1H, dd, J = 2.0, 7.6 Hz), 7.70-7.52 (7H, m), 7.43 (1H, d, J = 7.6 Hz), 7.30-7.26 (4H, m), 7.18-7.13 (2H, m), 5.13 (2H, s), 3.20 (2H, s), 0.95 (9H, s).

5 Example 2

2'-(4-amidinophenylcarbamoyl)-4-((2,2-dimethylpropyl)carbamoyl)-2-biphenylcarboxylic acid methanesulfonate

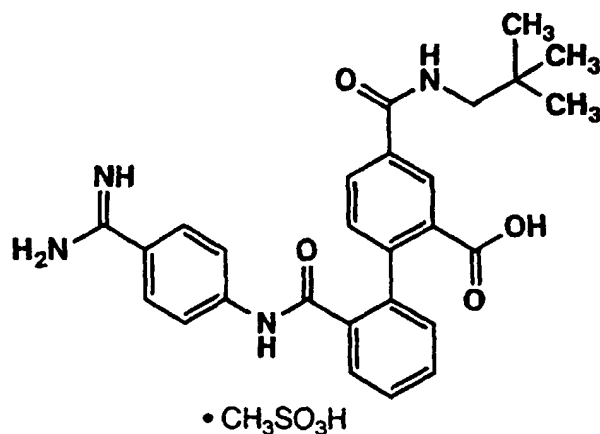
[0097]

10

15

20

25



30 [0098] 10% palladium carbon (80 mg) was added to a solution of the compound prepared in Example 1 (814 mg) in methanol (15 ml) under an atmosphere of argon at room temperature. Hydrogen substitution was done, and the mixture was stirred for 20 minutes at room temperature. The reaction mixture was filtered through celite (registered trade mark). 1N methanesulfonic acid in methanol (1.45 ml) was added to the filtrate, and the mixture was concentrated. The residue was crystallized with ether to give the present compound (820 mg) having the following physical data.

35

TLC : Rf 0.19 (Chloroform : Methanol : Water = 8 : 2 : 0.1) ;

NMR (d₆-DMSO) : δ 10.6 (1H, s), 9.18 (2H, br s), 8.91 (2H, br s), 8.56 (1H, t, J = 6.6 Hz), 8.31 (1H, d, J = 1.8 Hz), 7.99 (1H, dd, J = 1.8, 8.2 Hz), 7.74-7.69 (5H, m), 7.59-7.53 (2H, m), 7.33 (1H, d, J = 8.0 Hz), 7.31-7.26 (1H, m), 3.12 (2H, d, J = 6.6 Hz), 2.38 (3H, s), 0.90 (9H, s).

40

45

50

55

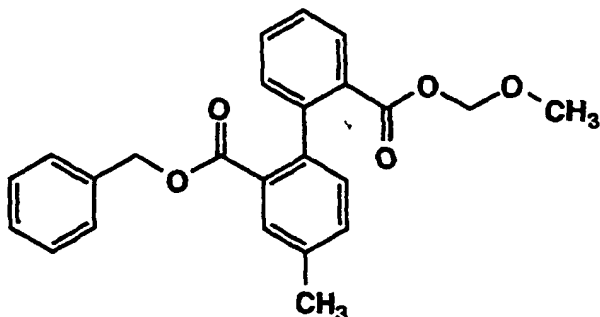
Reference Example 6

Methoxymethyl 2'-benzyloxycarbonyl-4'-methyl-2-biphenylcarboxylate

5 [0099]

10

15



20

[0100] Isopropylethylamine (488 μ l) was added to a solution of 2'-benzyloxycarbonyl-4'-methyl-2-biphenylcarboxylic acid (880 mg) in methylene chloride (8 ml) which was prepared by the same procedure as a series of reaction of Reference Example 4 \rightarrow Reference Example 5, using benzyl 2-trifluoromethylsulfonyloxy-5-methylbenzoate. The mixture was cooled to 0 $^{\circ}$ C, and methoxy chloride (212 μ l) was added to a solution. The mixture was stirred for 30 minutes. Water was added to the reaction mixture, and the solution was extracted with chloroform. The extract was washed with 1N hydrochloric acid and a saturated aqueous solution of sodium chloride, successively, dried over anhydrous sodium sulfate and concentrated to give the present compound (993 mg) having the following physical data.

30

TLC : Rf 0.41 (Hexane : Ethyl acetate = 8 : 2) ;

NMR (CDCl_3) : δ 7.98 (1H, dd, J = 8.0, 1.5 Hz), 7.86 (1H, s), 7.52-7.05 (10H, m), 5.18 (1H, d, J = 6.0 Hz), 5.12 (1H, d, J = 6.0 Hz), 5.04 (2H, s), 3.22 (3H, s), 2.43 (3H, s).

Example 3

35

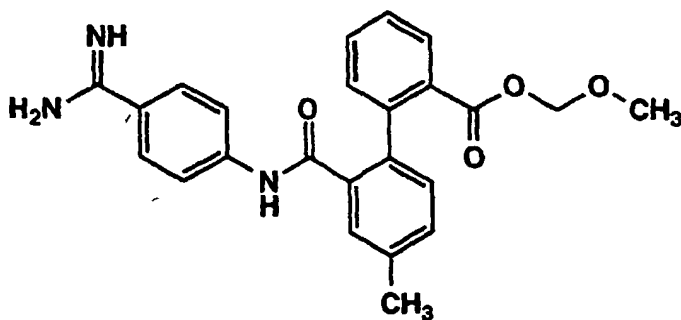
Methoxymethyl 2'-(4-amidinophenylcarbamoyl)-4'-methyl-2-biphenylcarboxylate

[0101]

40

45

50



55

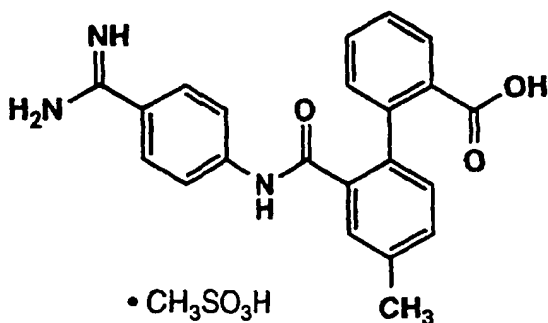
[0102] The present compound having the following physical data was obtained by the same procedure as a series of reaction of Example 2 (without a procedure of conversion to salt thereof) \rightarrow Example 1, using the compound prepared in Reference Example 6.

TLC : Rf 0.51 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1).

Example 4

2'-(4-amidinophenylcarbamoyl)-4'-methyl-2-biphenylcarboxylic acid methanesulfonate

[0103]



[0104] A solution of the compound prepared in Example 3 (340 mg) in 90% aqueous solution of trifluoroacetic acid (3 ml) was stirred for 2 hours at room temperature. The reaction mixture was concentrated. The residue was distilled off an azeotropic mixture with toluene, and was crystallized with a mixed solution of methanol and ether. The crystals were dissolved with a little of methanol. Methanesulfonic acid (53 μ l), and ethyl acetate was added to the solution. The mixture was stirred for 14 hours. The reaction mixture was filtered to give the present compound (182 mg) having the following physical data.

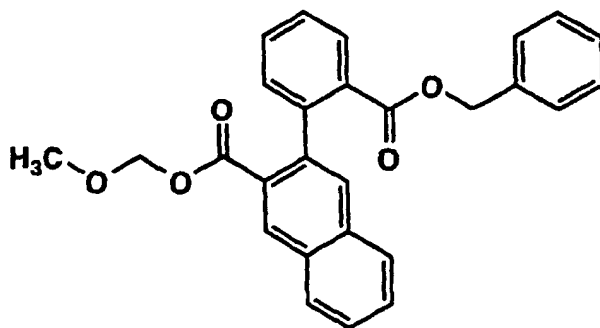
TLC : Rf 0.16 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d₆-DMSO) : δ 13.2-12.2 (1H, broad), 10.40 (1H, s), 9.14 (2H, brs), 8.87 (2H, brs), 7.80 (1H, d, J = 8 Hz), 7.74 (2H, d, J = 9 Hz), 7.67 (2H, d, J = 9 Hz), 7.49 (1H, td, J = 8 Hz, 2 Hz), 7.47 (1H, s), 7.43-7.33 (2H, m), 7.20 (1H, d, J = 8 Hz, 2 Hz), 7.13 (1H, d, J = 8 Hz), 2.43 (3H, s), 2.35 (3H, s).

Reference Example 7

Benzyl 2-(3-methoxymethoxycarbonylnaphthalen-2-yl)benzoate

[0105]



[0106] Benzyl bromide (160 μ l) and potassium carbonate (202 mg) were added to a solution of 2-(3-(methoxymeth-

oxycarbonyl)naphthalen-2-yl)benzoic acid (410 mg) which was prepared by the same procedure as a series of reaction of Reference Example 4 → Reference Example 5 using methoxymethyl 2-trifluoromethylsulfonyloxy-3-naphthalenecarboxylate, in dimethylformamide (5 ml). The mixture was stirred for 22 hours at room temperature. Water was added to the reaction mixture, and the solution was extracted with ethyl acetate. The extract was washed with water and a saturated aqueous solution of sodium chloride, successively, dried over anhydrous sodium sulfate and concentrated. The residue was purified by column chromatography on silica gel (hexane : ethyl acetate = 8 : 2) to give the title compound (498 mg) having the following physical data.

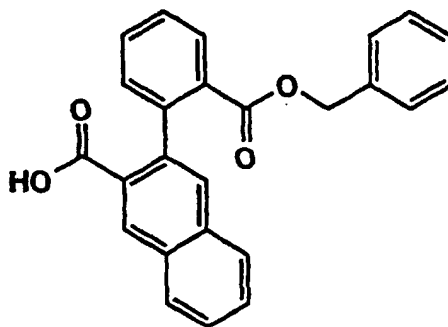
TLC : Rf 0.53 (Hexane : Ethyl acetate = 7 : 3) ;

NMR (CDCl₃) : δ 8.54 (1H, s), 8.10 (1H, dd, J = 8.0, 1.5 Hz), 7.94 (1H, d, J = 8.0 Hz), 7.80 (1H, d, J = 8.0 Hz), 7.64-7.53 (4H, m), 7.46 (1H, td, J = 8.0, 1.5 Hz), 7.32 (1H, dd, J = 8.0, 1.5 Hz), 7.17-7.01 (3H, m), 6.95-6.90 (2H, m), 5.24 (1H, d, J = 6.0 Hz), 5.18 (1H, d, J = 6.0 Hz), 5.05 (1H, d, J = 12 Hz), 4.95 (1H, d, J = 12 Hz), 3.26 (3H, s).

Reference Example 8

3-(2-benzyloxycarbonylphenyl)-2-naphthalenecarboxylic acid

[0107]



[0108] 1N Hydrochloric acid (2.3 ml) was added to a solution of the compound prepared in Reference Example 7 (490 mg) in dioxane (7 ml). The mixture was stirred for 5.5 hours at 50 °C. Water was added to the reaction mixture, and the solution was extracted with ethyl acetate. The extract was washed with a saturated aqueous solution of sodium chloride, dried over anhydrous sodium sulfate and concentrated. The residue was crystallized with hexane to give the title compound (423 mg) having the following physical data.

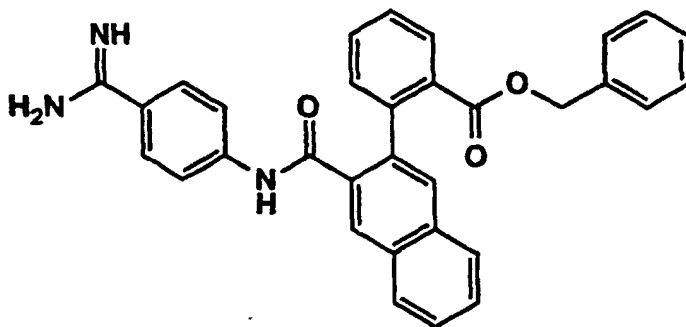
TLC : Rf 0.16 (Hexane : Ethyl acetate = 1 : 1) ;

NMR (CDCl₃) : δ 8.51 (1H, s), 8.08 (1H, dd, J = 8.0, 1.5 Hz), 7.91 (1H, d, J = 8.0 Hz), 7.78 (1H, d, J = 8.0 Hz), 7.65-7.42 (5H, m), 7.28 (1H, dd, J = 8.0, 1.5 Hz), 7.16-6.90 (5H, m), 5.05 (1H, d, J = 12 Hz), 4.95 (1H, d, J = 12 Hz).

Example 5

Benzyl 2-(3-(4-amidinophenylcarbamoyl)naphthalen-2-yl)benzoate

[0109]



[0110] The present compound having the following physical data was obtained by the same procedure as a series of reaction of Example 1, using the compound prepared in Reference Example 8.

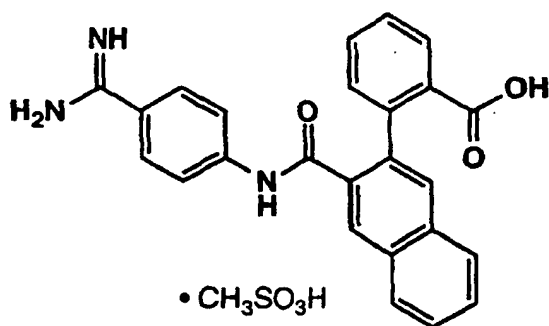
TLC : Rf 0.62 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (CD₃OD) : δ 8.18 (1H, s), 8.10-7.82 (3H, m), 7.78-7.52 (8H, m), 7.46 (1H, dd, J = 8 Hz, 2 Hz), 7.41 (1H, d, J = 8 Hz), 7.18-6.90 (5H, m), 5.06 (2H, s).

Example 6

2-(3-(4-amidinophenylcarbamoyl)naphthalen-2-yl)benzoic acid methanesulfonate

[0111]



[0112] The present compound having the following physical data was obtained by the same procedure as a series of reaction of Example 2, using the compound prepared in Example 5.

TLC : Rf 0.64 (Chloroform : Methanol : Water = 7 : 3 : 0.3) ;

NMR (d₆-DMSO) : δ 12.4-12.9 (1H, broad), 10.67 (1H, s), 9.20 (2H, s), 8.98 (2H, s), 8.28 (1H, s), 8.16-7.92 (2H, m), 7.87 (1H, d, J = 8 Hz), 7.79 (1H, s), 7.77 (4H, s), 7.70-7.50 (3H, m), 7.44 (1H, t, J = 8 Hz), 7.34 (1H, d, J = 8 Hz), 2.36 (3H, s).

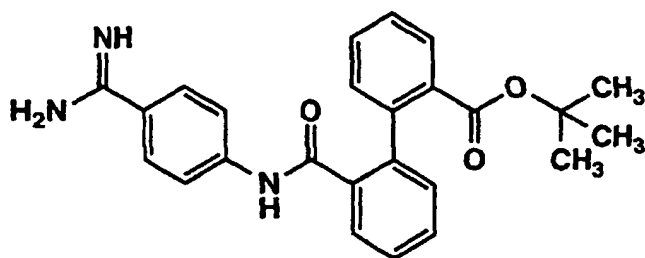
Example 7-7(115)

[0113] The following compounds were obtained by the same procedure as a series of reaction of Reference Example 4 (using 2-formylphenylboric acid or a corresponding derivatives) → Reference Example 5 → Example 1 (using 4-amidinoaniline or a corresponding derivatives), using the compound prepared in Reference Example 3 or a corresponding derivatives.

Example 7

10 t-Butyl 2'-(4-amidinophenylcarbamoyl)-2-biphenylcarboxylate

[0114]



25

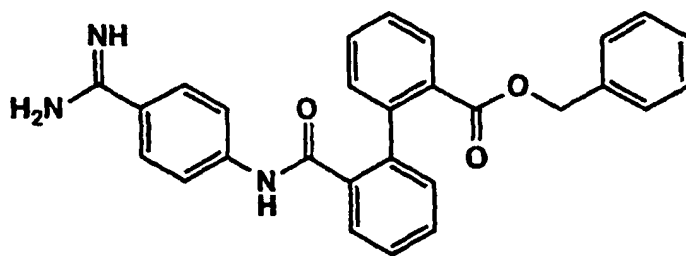
TLC : Rf 0.27 (Chloroform : Methanol : Water = 8 : 2 : 0.2) ;

30 NMR (CD₃OD) : δ 7.66-7.81 (2H, m), 7.69 (2H, d, J = 9.2 Hz), 7.50-7.60 (2H, m), 7.57 (2H, d, J = 9.2 Hz), 7.48 (1H, dt, J = 1.8, 7.6 Hz), 7.39 (1H, dt, J = 1.8, 7.6 Hz), 7.22-7.27 (2H, m), 1.34 (9H, s).

Example 7(1)

35 Benzyl 2'-(4-amidinophenylcarbamoyl)-2-biphenylcarboxylate

[0115]



50

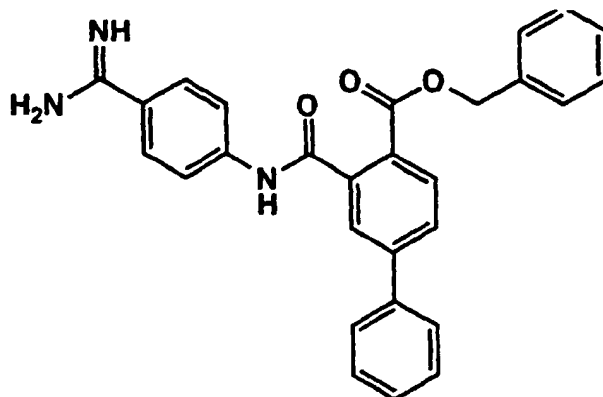
TLC : Rf 0.57 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

55 NMR (CD₃OD) : δ 7.85 (1H, dd, J = 8 Hz, 2 Hz), 7.68-7.62 (3H, m), 7.57-7.13 (13H, m), 5.13 (2H, s).

Example 7(2)

Benzyl 3-(4-amidinophenylcarbamoyl)-4-biphenylcarboxylate

5 [0116]



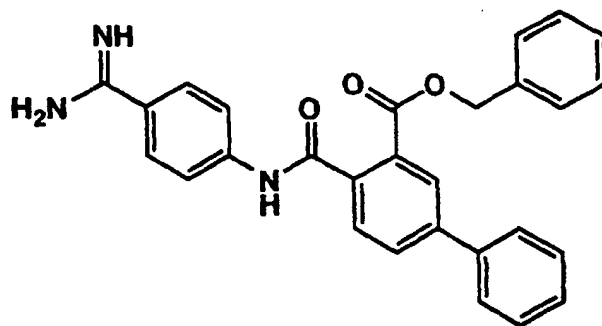
25

TLC : Rf 0.54 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;
 NMR(CD₃OD) : δ 8.12 (1H, d, J = 8Hz), 7.91-7.68 (8H, m), 7.55-7.40 (3H, m), 7.38-7.28 (2H, m), 7.26-7.16 (3H, m), 5.28 (2H, s).

30 Example 7(3)

Benzyl 4-(4-amidinophenylcarbamoyl)-3-biphenylcarboxylate

35 [0117]



50

TLC : Rf 0.51 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;
 NMR (CD₃OD) : δ 8.24 (1H, d, J = 2 Hz), 7.96 (1H, dt, J = 8 Hz, 2 Hz), 7.91-7.64 (7H, m), 7.56-7.41 (3H, m), 7.36-7.29 (2H, m), 7.24-7.16 (3H, m), 5.29 (2H, s).

55

Example 7(4)

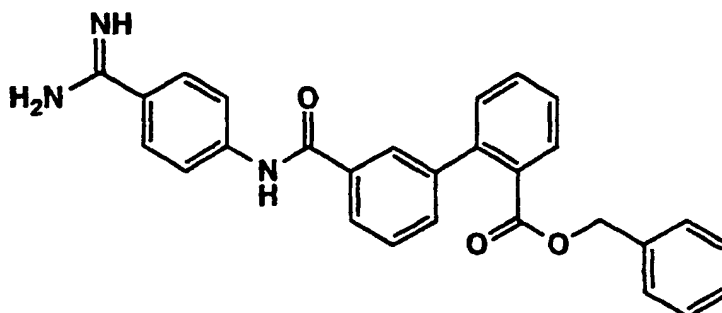
Benzyl 3'-(4-amidinophenylcarbamoyl)-2-biphenylcarboxylate

5 [0118]

10

15

20



25

TLC : Rf 0.57 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (CD₃OD) : δ 8.04 (2H, d, J = 9 Hz), 7.97-7.80 (3H, m), 7.85 (2H, d, J = 9 Hz), 7.64 (1H, td, J = 8Hz, 2 Hz), 7.55-7.43 (4H, m), 7.24-7.18 (3H, m), 7.11-7.06 (2H, m), 5.09 (2H, s).

Example 7(5)

Benzyl 2,3-dihydro-2,2-dimethyl-5-(2-(4-amidinophenylcarbamoyl)phenyl)-6-benzofurancarboxylate

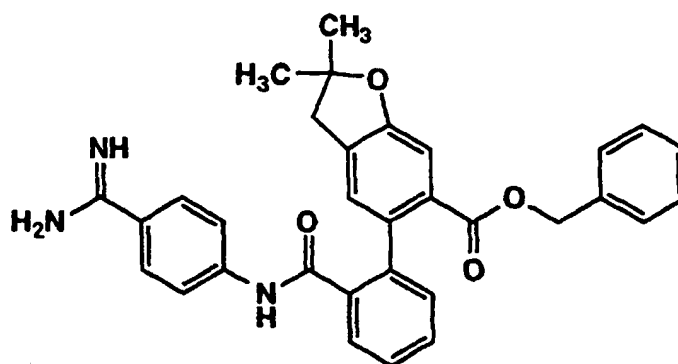
30

[0119]

35

40

45



50

TLC : Rf 0.44 (Chloroform : Methanol : Acetic acid = 20 : 2 : 1) ;

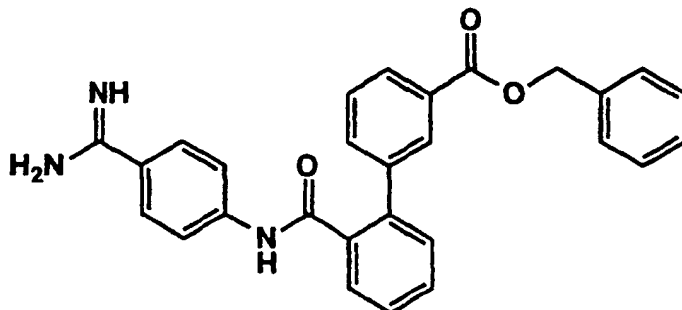
NMR (CD₃OD) : δ 7.72-7.39 (7H, m), 7.35-7.12 (6H, m), 7.08 (1H, s), 7.07 (1H, s), 5.12 (2H, s), 3.02 (2H, s), 1.43 (3H, brs), 1.38 (3H, brs).

55

Example 7(6)

Benzyl 2'-(4-amidinophenylcarbamoyl)-3-biphenylcarboxylate

[0120]



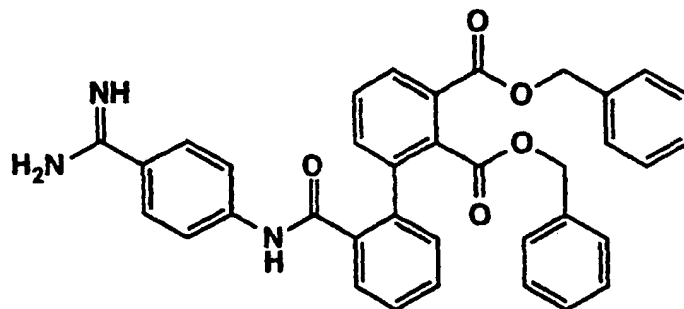
TLC : Rf 0.61 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (CD₃OD) : δ 8.17 (1H, s), 7.95 (1H, d, J = 8 Hz), 7.76-7.46 (10H, m), 7.45-7.30 (5H, m), 5.30 (2H, s).

Example 7(7)

Dibenzyl 2'-(4-amidinophenylcarbamoyl)-2,3-biphenyldicarboxylate

[0121]



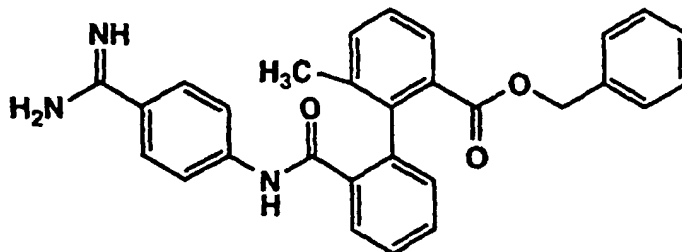
TLC : Rf 0.65 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d₆-DMSO) : δ 10.67 (1H, s), 9.50-8.95 (3H, broad), 7.91 (1H, dd, J = 8Hz, 2 Hz), 7.82-7.68 (5H, m), 7.68-7.46 (4H, m), 7.45-7.30 (5H, m), 7.30-7.16 (4H, m), 7.02-6.90 (2H, m), 5.24 (2H, s), 5.00-4.65 (2H, broad).

Example 7(8)

Benzyl 2'-(4-amidinophenylcarbamoyl)-6-methyl-2-biphenylcarboxylate

5 [0122]



20

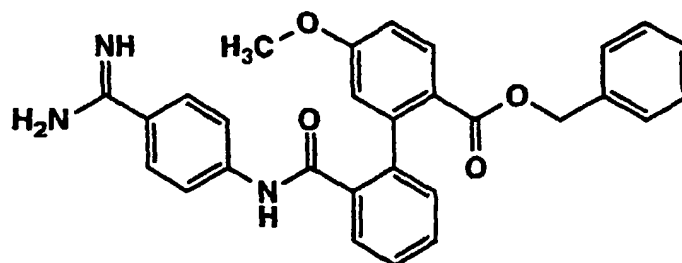
TLC : R_f 0.61 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;NMR (CD₃OD) : δ 7.72-7.62 (4H, m), 7.58-7.45 (4H, m), 7.42-7.22 (7H, m), 7.11-7.02 (1H, m), 5.22 (1H, d, J = 11 Hz), 5.15 (1H, d, J = 11 Hz), 1.98 (3H, s).

25

Example 7(9)

Benzyl 2'-(4-amidinophenylcarbamoyl)-5-methoxy-2-biphenylcarboxylate

30 [0123]



45

TLC : R_f 0.32 (Chloroform : Methanol : Water = 8 : 2 : 0.2) ;NMR (d₆-DMSO) : δ 10.74 (1H, s), 9.07 (3H, br.s), 7.80 (1H, d, J = 8.8 Hz), 7.74 (2H, d, J = 9.4 Hz), 7.70 (2H, d, J = 9.4 Hz), 7.62 (1H, dd, J = 2.2, 7.0 Hz), 7.47-7.54 (2H, m), 7.23-7.32 (4H, m), 7.03-7.07 (2H, m), 6.96 (1H, dd, J = 2.6, 8.8 Hz), 6.82 (1H, d, J = 2.6 Hz), 4.99 (2H, s), 3.80 (3H, s).

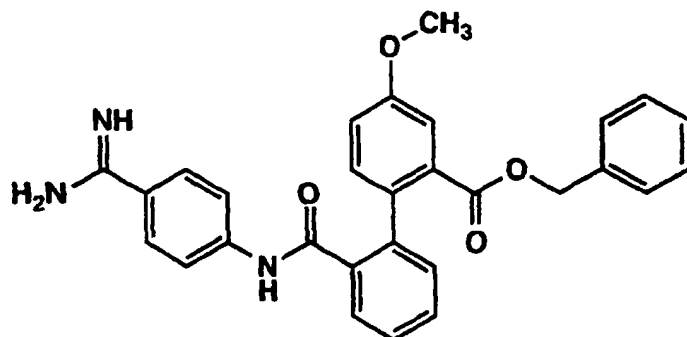
50

55

Example 7(10)

Benzyl 2'-(4-amidinophenylcarbamoyl)-4-methoxy-2-biphenylcarboxylate

5 [0124]



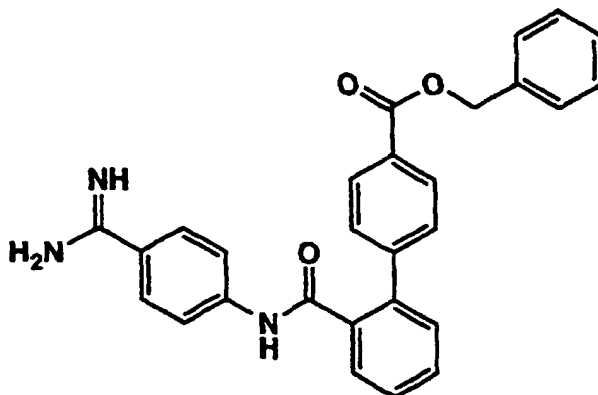
TLC : Rf 0.30 (Chloroform : Methanol : Water = 8 : 2 : 0.2) ;

NMR (CD₃OD) : δ 7.67 (2H, d, J = 8.8 Hz), 7.63 (1H, m), 7.54 (2H, d, J = 8.8 Hz), 7.45-7.49 (2H, m), 7.36 (1H, d, J = 2.6 Hz), 7.25-7.30 (4H, m), 7.06-7.23 (4H, m), 5.14 (2H, s), 3.81 (3H, s).

Example 7(11)

Benzyl 2'-(4-amidinophenylcarbamoyl)-4-biphenylcarboxylate

[0125]



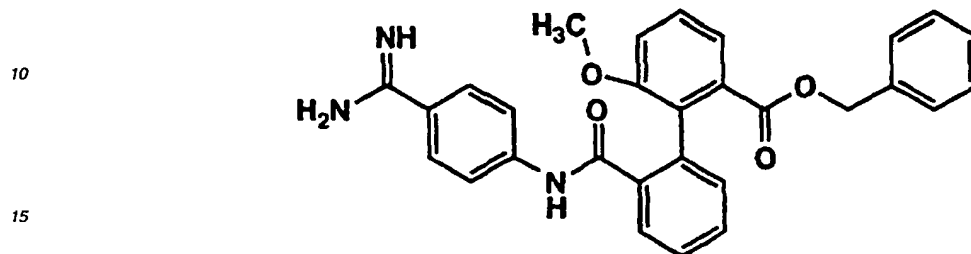
TLC : Rf 0.41 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (CD₃OD) : δ 8.01 (2H, d, J = 8.5 Hz), 7.70 (4H, s), 7.68-7.50 (6H, m), 7.46-7.32 (5H, m), 5.33 (2H, s).

Example 7(12)

Benzyl 2'-(4-amidinophenylcarbamoyl)-6-methoxy-2-biphenylcarboxylate

5 [0126]



20

TLC : Rf 0.34 (Chloroform : Methanol : Water = 8 : 2 : 0.2) ;

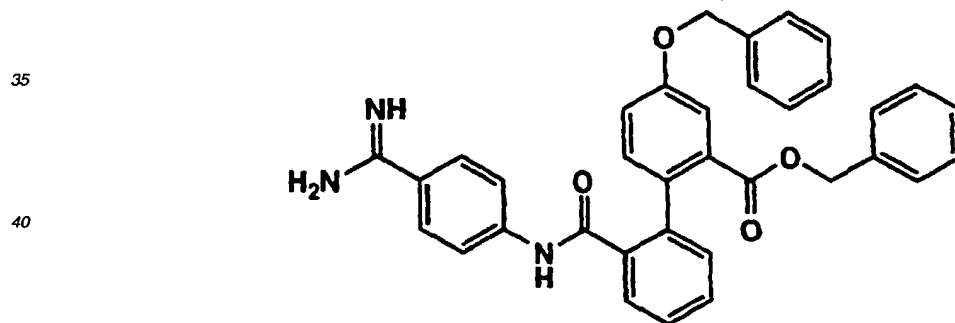
NMR (CD₃OD) : δ 7.67 (2H, d, J = 8.8 Hz), 7.67 (1H, m), 7.52 (2H, d, J = 8.8 Hz), 7.38-7.50 (4H, m), 7.28-7.34 (3H, m), 7.04-7.20 (4H, m), 5.15 (1H, d, J = 12.0 Hz), 5.08 (1H, d, J = 12.0 Hz), 3.63 (3H, s).

25

Example 7(13)

Benzyl 2'-(4-amidinophenylcarbamoyl)-4-benzyloxy-2-biphenylcarboxylate

30 [0127]



45

TLC : Rf 0.41 (Chloroform : Methanol : Water = 8 : 2 : 0.2) ;

NMR (CD₃OD) : δ 7.67 (2H, d, J = 8.8 Hz), 7.63 (1H, m), 7.54 (2H, d, J = 8.8 Hz), 7.14-7.49 (16H, m), 5.12 (2H, s), 5.10 (2H, s).

50

55

Example 7(14)

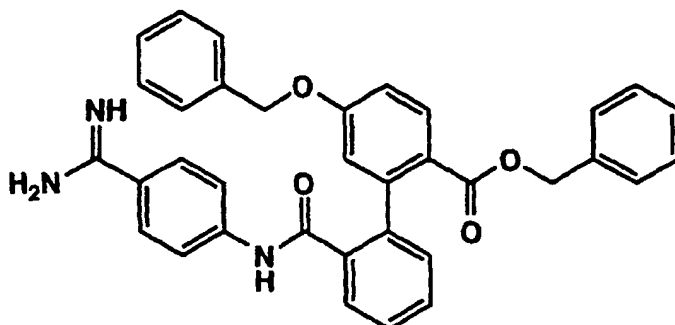
Benzyl 2'-(4-amidinophenylcarbamoyl)-5-benzyloxy-2-biphenylcarboxylate

5 [0128]

10

15

20



25 TLC : Rf 0.43 (Chloroform : Methanol : Water = 8 : 2 : 0.2) ;
 NMR (d_6 -DMSO) : δ 10.50 (1H, s), 9.21 (1.5H, s), 8.96 (1.5H, s), 7.81 (1H, d, J = 8.4 Hz), 7.76 (4H, s), 7.65 (1H, m), 7.48-7.55 (2H, m), 7.24-7.40 (9H, m), 7.03-7.08 (3H, m), 6.93 (1H, d, J = 2.6 Hz), 5.15 (2H, s), 5.00 (2H, s).

Example 7(15)

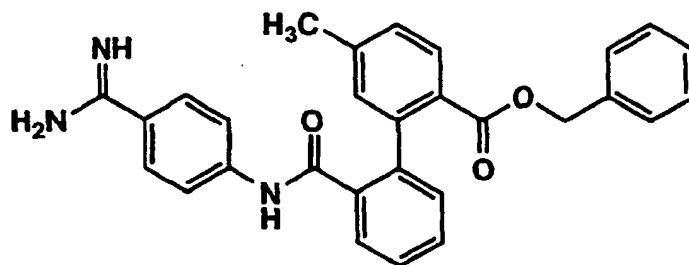
30 Benzyl 2'-(4-amidinophenylcarbamoyl)-5-methyl-2-biphenylcarboxylate

[0129]

35

40

45



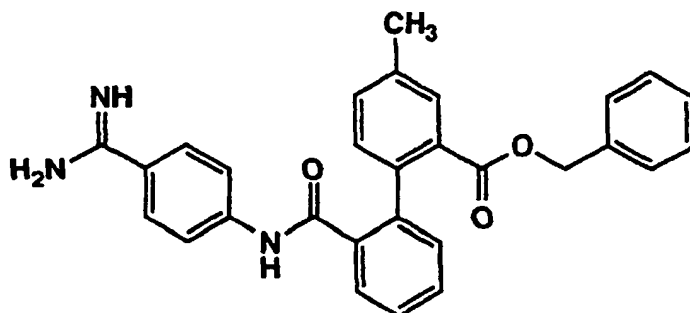
50 TLC : Rf 0.44 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;
 NMR (d_6 -DMSO) : δ 9.11 (2H, s), 8.87 (2H, s), 7.61 (4H, t, J = 8.0 Hz), 7.52 (1H, dd, J = 2.0, 8.0 Hz), 7.45 (1H, d, J = 8.5 Hz), 7.42 (1H, t, J = 8.0 Hz), 7.38 (1H, t, J = 8.0 Hz), 7.20 - 7.03 (5H, m), 7.01 (1H, brs), 6.92 (1H, d, J = 7.5 Hz), 6.91 (1H, d, J = 8.0 Hz), 4.87 (2H, s), 2.22 (3H, s).

55

Example 7(16)

Benzyl 2'-(4-amidinophenylcarbamoyl)-4-methyl-2-biphenylcarboxylate

5 [0130]



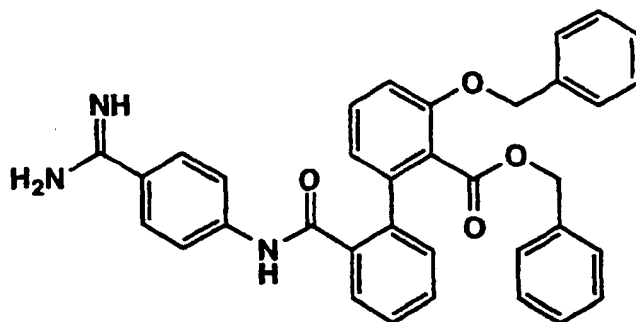
20

TLC : Rf 0.44 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;
 25 NMR (d₆-DMSO) : δ 9.15 (2H, brs), 8.89 (2H, s), 7.66 (4H, brs), 7.60 - 7.47 (2H, m), 7.45 (1H, brt, J = 8.0 Hz), 7.31 (1H, d, J = 8.0 Hz), 7.26 - 7.02 (5H, m), 7.02 - 6.90 (2H, m), 4.93 (2H, s), 2.26 (3H, s).

Example 7(17)

30 Benzyl 2'-(4-amidinophenylcarbamoyl)-3-benzyloxy-2-biphenylcarboxylate

[0131]



45

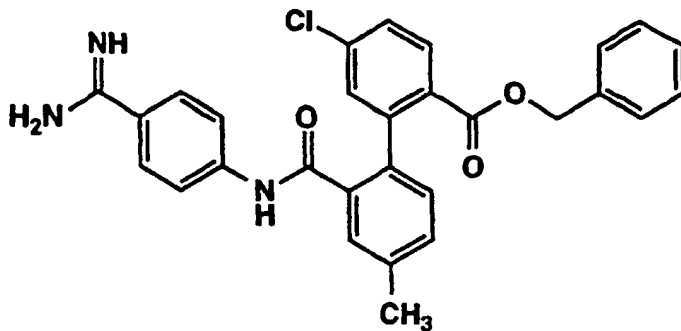
50 TLC : Rf 0.43 (Chloroform : Methanol : Water = 8 : 2 : 0.2) ;
 NMR (CD₃OD) : δ 7.67 (1H, m), 7.66 (2H, d, J = 8.8 Hz), 7.45-7.56 (2H, m), 7.53 (2H, d, J = 8.8 Hz), 7.13-7.39 (12H, m), 7.09 (1H, d, J = 8.4 Hz), 6.82 (1H, d, J = 6.8 Hz), 5.15 (2H, s), 4.86 (2H, s).

55

Example 7(18)

Benzyl 2'-(4-amidinophenylcarbamoyl)-4'-methyl-5-chloro-2-biphenylcarboxylate

[0132]



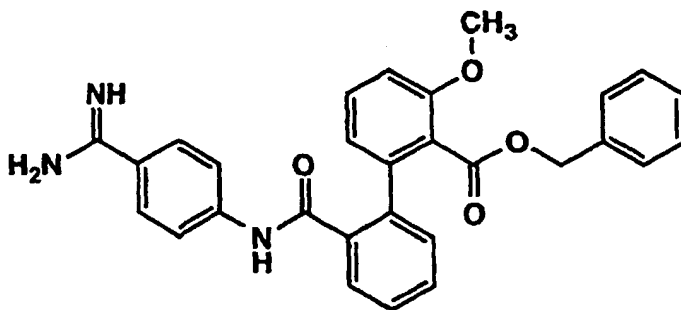
TLC : Rf 0.42 (Chloroform : Methanol = 4 : 1) ;

NMR (CDCl₃) : δ 9.29 (1H, s), 8.80 (2H, s), 8.59 (2H, s), 7.72 (2H, d, J = 8.2 Hz), 7.49 (1H, s), 7.40 (2H, d, J = 8.2 Hz), 7.4-7.1 (9H, m), 6.94 (1H, d, J = 8.2 Hz), 5.10 (2H, s), 2.36 (3H, s).

Example 7(19)

Benzyl 2'-(4-amidinophenylcarbamoyl)-3-methoxy-2-biphenylcarboxylate

[0133]



TLC : Rf 0.27 (Chloroform : Methanol : Water = 8 : 2 : 0.2) ;

NMR (CD₃OD) : δ 7.67 (2H, d, J = 8.8 Hz), 7.66 (1H, m), 7.43-7.55 (2H, m), 7.52 (2H, d, J = 8.8 Hz), 7.27-7.40 (4H, m), 7.16-7.22 (3H, m), 7.03 (1H, d, J = 8.4 Hz), 6.80 (1H, d, J = 7.0 Hz), 5.15 (2H, s), 3.84 (3H, s).

Example 7(20)

Benzyl 2'-(4-amidinophenylcarbamoyl)-4'-methyl-4-methoxy-2-biphenylcarboxylate

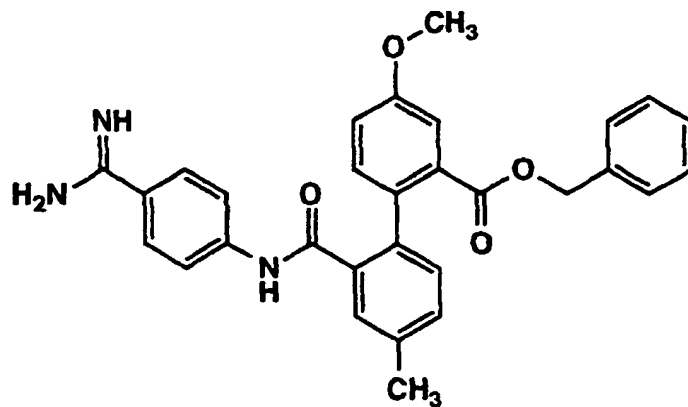
5 [0134]

10

15

20

25



30

TLC : Rf 0.34 (Chloroform : Methanol = 4 : 1) ;

NMR (CDCl₃) : δ 8.95 (2H, brs), 8.44 (1H, brs), 7.72 (2H, brs), 7.45 (1H, s), 7.4-7.3 (6H, m), 7.17 (2H, d, J = 6.4 Hz), 7.07 (1H, d, J = 8.4 Hz), 6.96 (1H, s), 6.90 (2H, d, J = 8.8 Hz), 5.17 (2H, s), 3.74 (3H, s), 2.40 (3H, s).

Example 7(21)

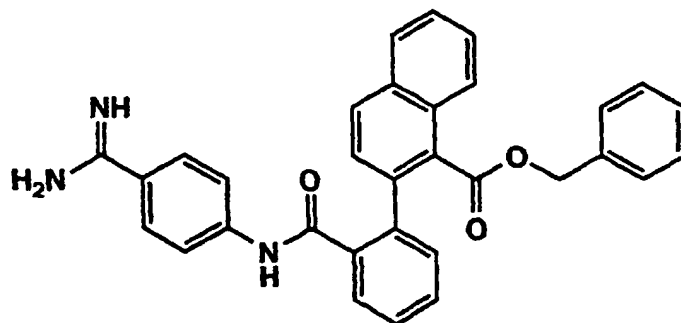
Benzyl 2-(2-(4-amidinophenylcarbamoyl)phenyl)-1-naphthalenecarboxylate

35 [0135]

40

45

50



55

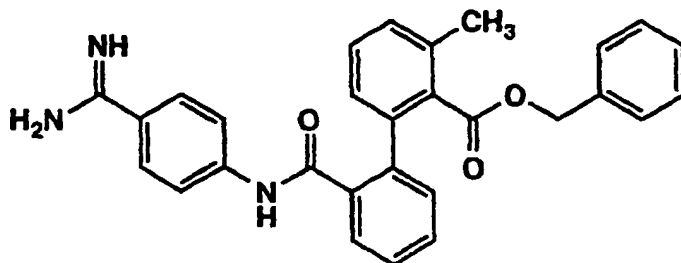
TLC : Rf 0.34 (Chloroform : Methanol : Water = 8 : 2 : 0.2) ;

NMR (d₆-DMSO) : δ 10.62 (1H, s), 9.09 (3H, br.s), 7.98-8.05 (2H, m), 7.78-7.90 (2H, m), 7.73 (4H, s), 7.57-7.63 (4H, m), 7.46 (1H, d, J = 8.4 Hz), 7.35 (1H, m), 7.26-7.29 (3H, m), 7.08-7.12 (2H, m), 5.16 (2H, br.s).

Example 7(22)

Benzyl 2'-(4-amidinophenylcarbamoyl)-3-methyl-2-biphenylcarboxylate

[0136]



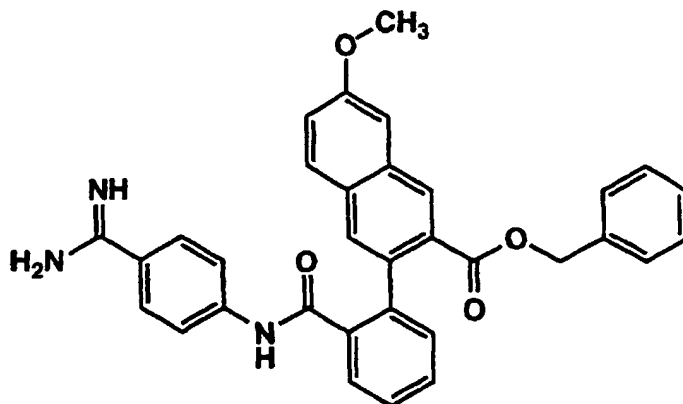
TLC : Rf 0.56 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d_6 -DMSO) : δ 9.09 (2H, brs), 8.82 (1H, s), 8.33 (2H, brs), 7.82 - 7.60 (3H, m), 7.52 - 7.03 (12H, m), 6.98 (1H, dd, J = 1.0, 8.5 Hz), 5.15 (1H, d, J = 10 Hz), 5.03 (1H, d, J = 10 Hz), 2.40 (3H, s).

Example 7(23)

Benzyl 3-(2-(4-amidinophenylcarbamoyl)phenyl)-7-methoxy-2-naphthalenecarboxylate

[0137]



TLC : Rf 0.48 (Chloroform : Methanol : Water = 10 : 3 : 0.2) ;

NMR (d_6 -DMSO) : δ 10.53 (1H, br.s), 9.08 (3H, br.s), 8.33 (1H, s), 7.89 (1H, d, J = 9.2 Hz), 7.7-7.4 (10H, m), 7.4-7.2 (4H, m), 7.2-7.0 (2H, m), 5.06 (2H, br.s), 3.87 (3H, s).

Example 7(24)

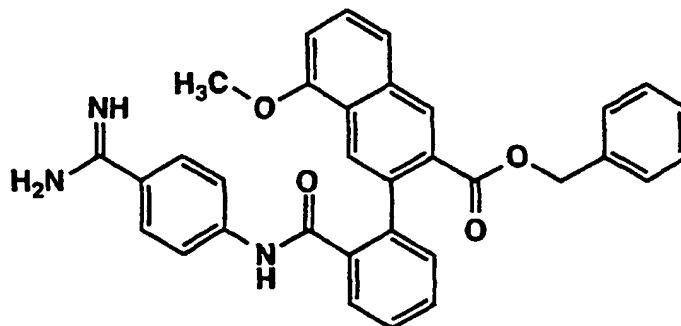
Benzyl 3-(2-(4-amidinophenylcarbamoyl)phenyl)-5-methoxy-2-naphthalenecarboxylate

5 [0138]

10

15

20



TLC : Rf 0.42 (Chloroform : Methanol : Water = 10 : 3 : 0.2) ;
 NMR (d₆-DMSO) : δ 10.56 (1H, s), 9.06 (3H, br.s), 8.38 (1H, s), 8.02 (1H, s), 7.8-7.4 (10H, m), 7.3-7.2 (3H, m), 7.2-7.0 (3H, m), 5.07 (2H, s), 3.94 (3H, s).

Example 7(25)

Dibenzyl 2'-(4-amidinophenylcarbamoyl)-2, 4-biphenyldicarboxylate

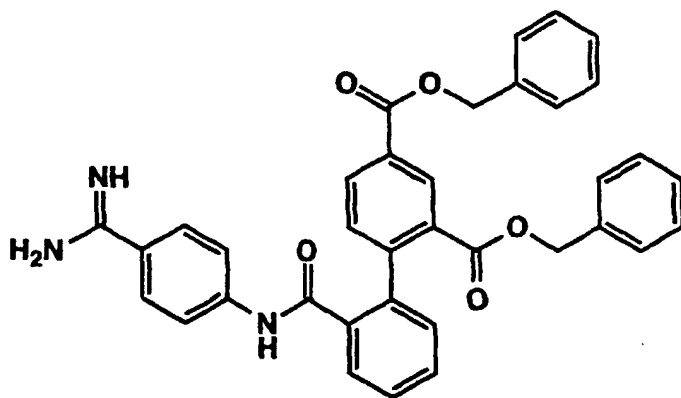
30

[0139]

35

40

45



50

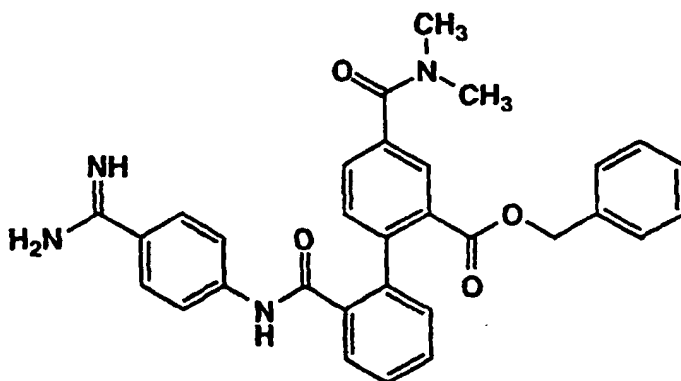
55

TLC : Rf 0.45 (Chloroform : Methanol : Water = 8 : 2 : 0.2) ;
 NMR (CD₃OD) : δ 8.50 (1H, d, J = 1.8 Hz), 8.18 (1H, dd, J = 1.8, 8.0 Hz), 7.67 (2H, d, J = 9.0 Hz), 7.61 (2H, d, J = 9.0 Hz), 7.10-7.54 (15H, m), 5.37 (2H, s), 5.11 (2H, s).

Example 7(26)

Benzyl 2'-(4-amidinophenylcarbamoyl)-4-dimethylcarbamoyl-2-biphenylcarboxylate

[0140]



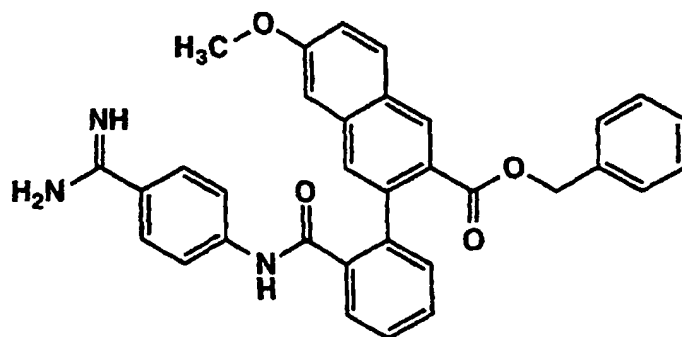
TLC : Rf 0.30 (Chloroform : Methanol : Water = 8 : 2 : 0.2) ;

NMR (CD₃OD) : δ 7.90 (1H, d, J = 1.8 Hz), 7.50-7.70 (8H, m), 7.42 (1H, d, J = 8.0 Hz), 7.25-7.31 (4H, m), 7.12-7.16 (2H, m), 5.12 (2H, s), 3.09 (3H, s), 2.92 (3H, s).

Example 7(27)

Benzyl 3-(2-(4-amidinophenylcarbamoyl)phenyl)-6-methoxy-2-naphthalenecarboxylate

[0141]



TLC : Rf 0.51 (Chloroform : Methanol : Water = 10 : 3 : 0.2).

Example 7(28)

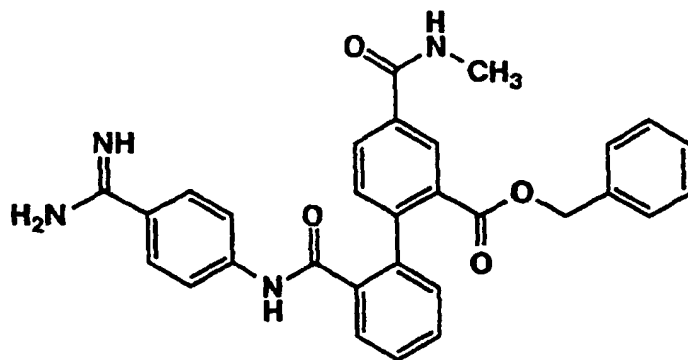
Benzyl 2'-(4-amidinophenylcarbamoyl)-4-methylcarbamoyl-2-biphenylcarboxylate

5 [0142]

10

15

20



25

TLC : Rf 0.24 (Chloroform : Methanol : Water = 8 : 2 : 0.2) ;

NMR (CD₃OD) : δ 8.32 (1H, d, J = 1.8 Hz), 7.96 (1H, dd, J = 1.8, 8.0 Hz), 7.67 (2H, d, J = 8.8 Hz), 7.65 (1H, m), 7.58 (2H, d, J = 8.8 Hz), 7.49-7.55 (2H, m), 7.42 (1H, d, J = 8.0 Hz), 7.24-7.30 (4H, m), 7.13-7.18 (2H, m), 5.16 (2H, s), 2.91 (3H, s).

Example 7(29)

30

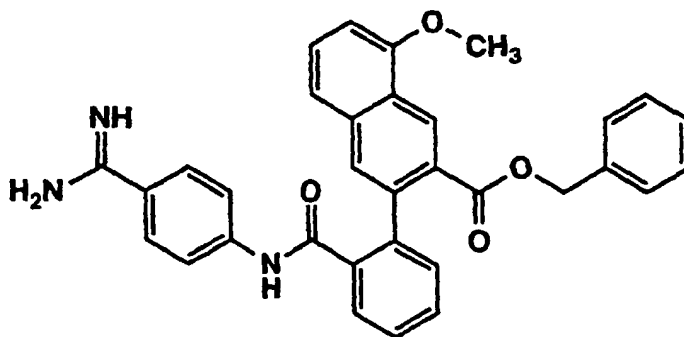
Benzyl 3-(2-(4-amidinophenylcarbamoyl)phenyl)-8-methoxy-3-naphthalenecarboxylate

[0143]

35

40

45



50

TLC : Rf 0.43 (Chloroform : Methanol : Water = 10 : 3 : 0.2) ;

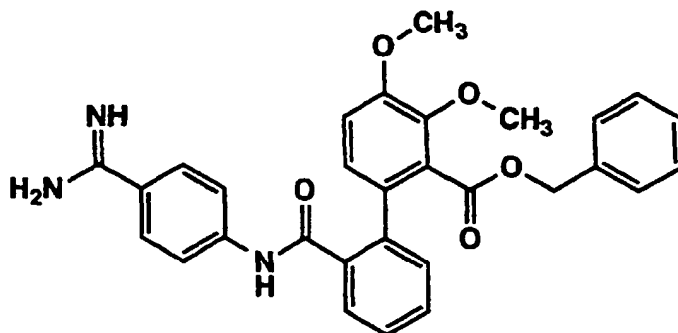
NMR (d₆-DMSO) : δ 10.57 (1H, s), 9.3-8.8 (3H, br), 8.62 (1H, s), 7.80 (1H, s), 7.8-7.4 (10H, m), 7.4-7.2 (3H, m), 7.2-7.0 (3H, m), 5.07 (2H, br.s), 3.98 (3H, s).

55

Example 7(30)

Benzyl 2'-(4-amidinophenylcarbamoyl)-3,4-dimethoxy-2-biphenylcarboxylate

5 [0144]



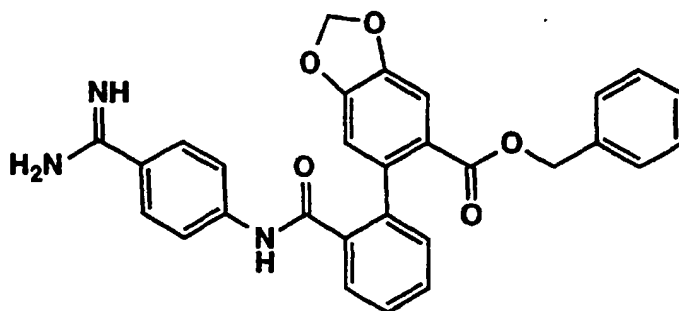
TLC : Rf 0.70 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

25 NMR (CD₃OD) : δ 7.71-7.62 (3H, m), 7.54 (2H, d, J = 9.0 Hz), 7.50 (1H, td, J = 7.5 Hz, 1.5 Hz), 7.43 (1H, td, J = 7.5 Hz, 1.5 Hz), 7.33-7.16 (6H, m), 7.06 (1H, d, J = 9.0 Hz), 6.94 (1H, d, J = 9.0 Hz), 5.17 (2H, s), 3.80 (3H, s), 3.77 (3H, s).

Example 7(31)

Benzyl 6-(2-(4-amidinophenylcarbamoyl)phenyl)-1,2-methylenedioxybenzene -5-carboxylate

30 [0145]



TLC : Rf 0.70 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

50 NMR (CD₃OD) : δ 7.69 (2H, d, J = 9.0 Hz), 7.62-7.55 (3H, m), 7.51-7.41 (2H, m), 7.31-7.22 (4H, m), 7.22-7.10 (3H, m), 6.72 (1H, s), 6.03 and 6.00 (2H, brs), 5.08 (2H, s).

Example 7(32)

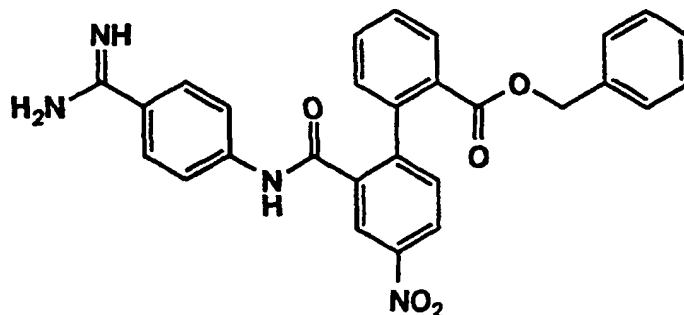
Benzyl 2'-(4-amidinophenylcarbamoyl)-4'-nitro-2-biphenylcarboxylate

5 [0146]

10

15

20



25

TLC : Rf 0.62 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (CD₃OD) : δ 8.32 (1H, d, J = 2.5 Hz), 8.19 (1H, dd, J = 8.5 Hz, 2.5 Hz), 8.01-7.96 (1H, m), 7.71 (2H, d, J = 9.0 Hz), 7.63 (2H, d, J = 9.0 Hz), 7.60 (1H, td, J = 7.5 Hz, 1.5 Hz), 7.48 (1H, td, J = 7.5 Hz, 1.5 Hz), 7.44 (1H, d, J = 8.5 Hz), 7.33 (1H, dd, J = 7.5 Hz, 1.5 Hz), 7.24-7.66 (5H, m), 5.06 and 5.04 (2H, s).

Example 7(33)

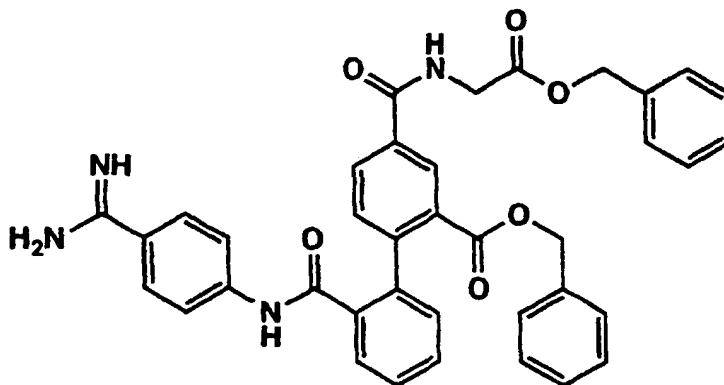
30 Benzyl 2'-(4-amidinophenylcarbamoyl)-4-((benzyloxycarbonylmethyl) carbamoyl)-2-biphenylcarboxylate

[0147]

35

40

45



50

55

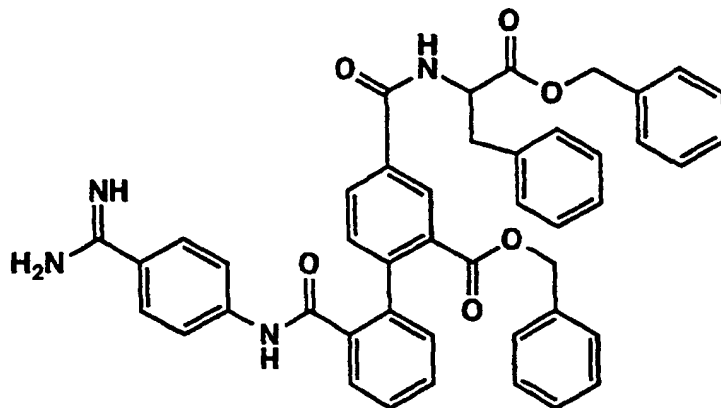
TLC : Rf 0.40 (Chloroform : Methanol : Water = 8 : 2 : 0.2) ;

NMR (CD₃OD) : δ 8.37 (1H, d, J = 1.8 Hz), 8.00 (1H, dd, J = 1.8, 8.0 Hz), 7.67 (2H, d, J = 9.2 Hz), 7.66 (1H, m), 7.59 (2H, d, J = 9.2 Hz), 7.50-7.55 (2H, m), 7.44 (1H, d, J = 8.0 Hz), 7.25-7.37 (9H, m), 7.13-7.18 (2H, m), 5.20 (2H, s), 5.14 (2H, s), 4.16 (2H, s).

Example 7(34)

Benzyl 2'-(4-amidinophenylcarbamoyl)-4-((1-benzoyloxycarbonyl-2-phenylethyl)carbamoyl)-2-biphenylcarboxylate

[0148]



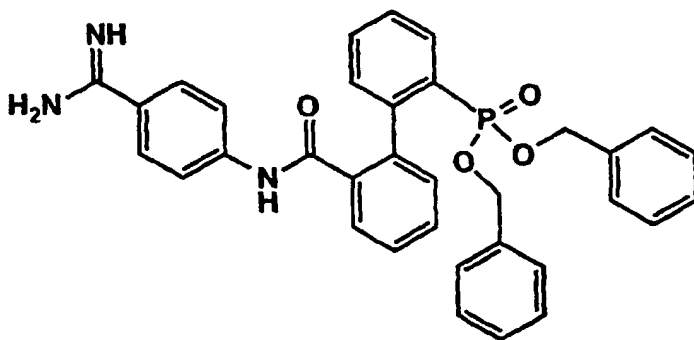
TLC : Rf 0.44 (Chloroform : Methanol : Water = 8 : 2 : 0.2) ;

NMR (CD₃OD) : δ 8.23 (1H, d, J = 1.8 Hz), 7.86 (1H, dd, J = 1.8, 7.8 Hz), 7.67 (2H, d, J = 9.0 Hz), 7.66 (1H, m), 7.59 (2H, d, J = 9.0 Hz), 7.49-7.54 (2H, m), 7.39 (1H, d, J = 7.8 Hz), 7.27-7.29 (8H, m), 7.18-7.20 (8H, m), 5.15 (2H, s), 5.13 (2H, s), 4.83 (1H, dd, J = 6.2, 9.2 Hz), 3.27 (1H, dd, J = 6.2, 13.8 Hz), 3.10 (1H, dd, J = 9.2, 13.8 Hz).

Example 7(35)

Dibenzyl 2'-(4-amidinophenylcarbamoyl)-2-biphenylphosphorate

[0149]



TLC : Rf 0.80 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (CD₃OD) : δ 7.96-7.84 (1H, m), 7.68-7.20 (21H, m), 4.90-4.82 (4H, m).

Example 7(36)

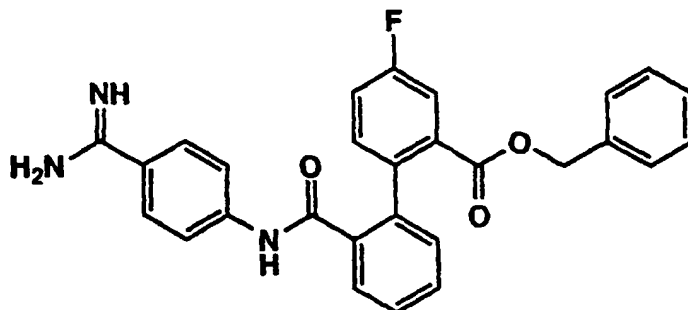
Benzyl 2'-(4-amidinophenylcarbamoyl)-4-fluoro-2-biphenylcarboxylate

5 [0150]

10

15

20



25

Example 7(37)

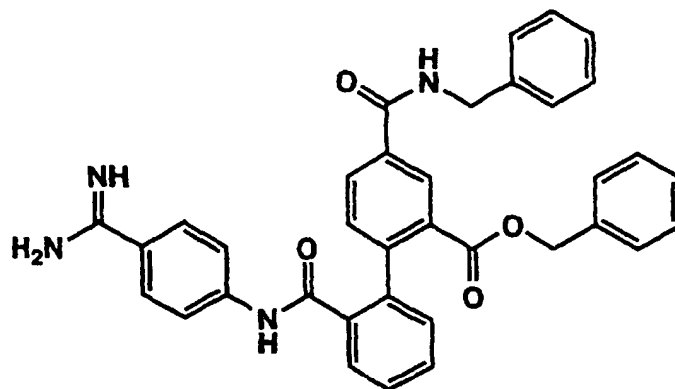
Benzyl 2'-(4-amidinophenylcarbamoyl)-4-benzylcarbamoyl-2-biphenylcarboxylate

30 [0151]

35

40

45



50

TLC : Rf 0.22 (Chloroform : Methanol : Water = 8 : 2 : 0.2) ;

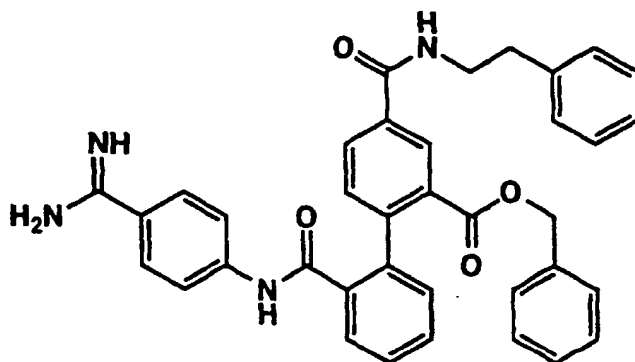
NMR (CD₃OD) : δ 8.37 (1H, d, J = 1.8 Hz), 8.00 (1H, dd, J = 1.8, 8.0 Hz), 7.65-7.69 (3H, m), 7.59 (2H, d, J = 9.2 Hz), 7.50-7.55 (2H, m), 7.42 (1H, d, J = 8.0 Hz), 7.24-7.34 (9H, m), 7.13-7.17 (2H, m), 5.13 (2H, s), 4.56 (2H, s).

55

Example 7(38)

Benzyl 2'-(4-amidinophenylcarbamoyl)-4-phenethylcarbamoyl-2-biphenylcarboxylate

5 [0152]

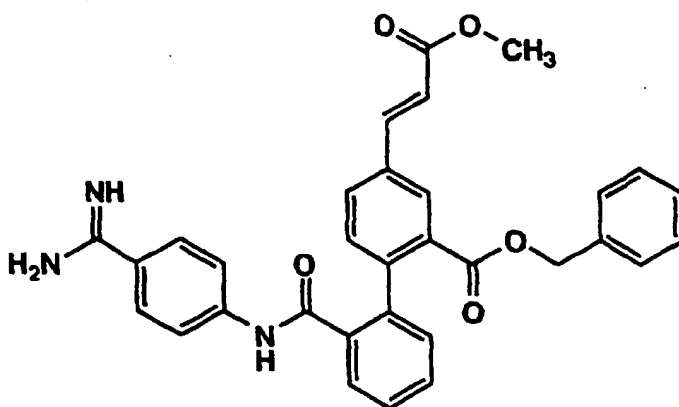


25 TLC : Rf 0.55 (Chloroform : Methanol : Water = 7 : 3 : 0.3) ;
 NMR (CD₃OD) : δ 8.28 (1H, d, J = 2.0 Hz), 7.92 (1H, dd, J = 2.0, 8.0 Hz), 7.66-7.70 (3H, m), 7.59 (2H, d, J = 9.2 Hz), 7.49-7.54 (2H, m), 7.41 (1H, d, J = 8.0 Hz), 7.13-7.30 (11H, m), 5.13 (2H, s), 3.58 (2H, t, J = 7.0 Hz), 2.89 (2H, t, J = 7.0 Hz).

30 Example 7(39)

Benzyl 2'-(4-amidinophenylcarbamoyl)-4-((1E)-2-methoxycarbonyl-ethenyl)-2-biphenylcarboxylate

35 [0153]

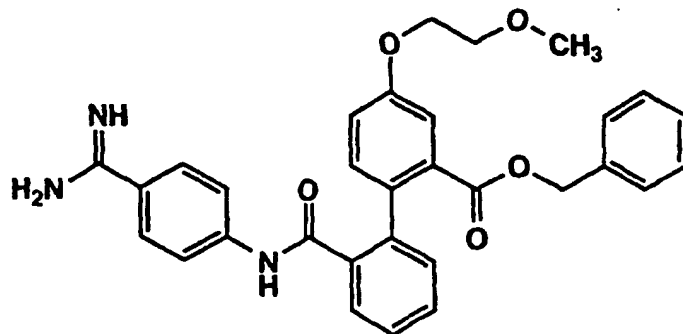


50
 55 TLC : Rf 0.32 (Chloroform : Methanol = 4 : 1) ;
 NMR (CDCl₃+CD₃OD) : δ 7.97 (1H, s), 7.8-7.5 (6H, m), 7.6-7.4 (2H, m), 7.4-7.2 (7H, m), 7.11 (1H, d, J = 6.6 Hz), 6.46 (1H, d, J = 16.2 Hz), 5.24 (2H, d, J = 5.6 Hz), 3.80 (3H, s).

Example 7(40)

Benzyl 2'-(4-amidinophenylcarbamoyl)-4-(2-methoxyethoxy)-2-biphenylcarboxylate

5 [0154]



20

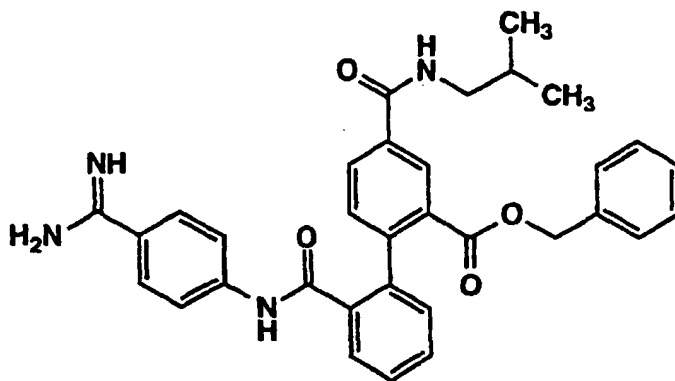
TLC : Rf 0.62 (Chloroform : Methanol : Water = 10 : 3 : 0.2) ;

25 NMR (d_6 -DMSO) : δ 10.47 (1H, br.s), 9.11 (3H, br.s), 7.8-7.4 (3H, m), 7.73 (4H, like s), 7.4-7.1 (7H, m), 7.1-7.0 (2H, m), 5.01 (2H, s), 4.12 (2H, t, J = 4.4 Hz), 3.64 (2H, t, J = 4.4 Hz), 3.33 (3H, s).

Example 7(41)

30 Benzyl 2'-(4-amidinophenylcarbamoyl)-4-((2-methylpropyl)carbamoyl)-2-biphenylcarboxylate

[0155]



35

40

45

50

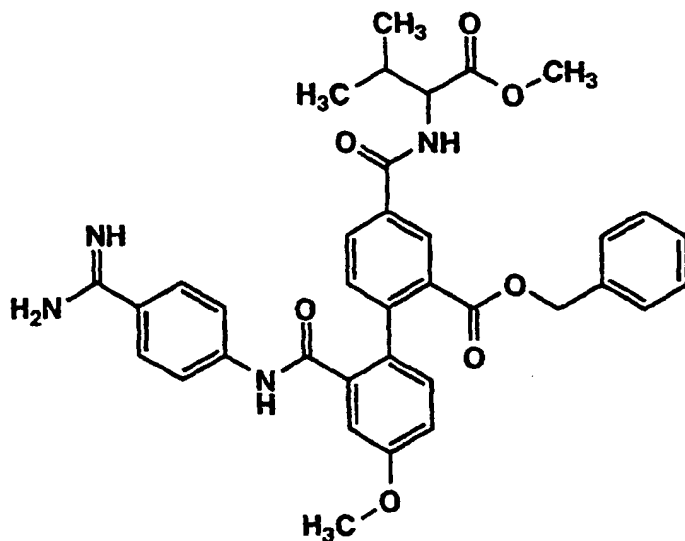
TLC : Rf 0.26 (Chloroform : Methanol : Water = 8 : 2 : 0.2) ;

55 NMR (CD_3OD) : δ 8.33 (1H, d, J = 1.6 Hz), 7.97 (1H, dd, J = 1.6, 8.0 Hz), 7.65-7.70 (3H, m), 7.59 (2H, d, J = 8.8 Hz), 7.50-7.54 (2H, m), 7.42 (1H, d, J = 8.0 Hz), 7.26-7.29 (4H, m), 7.15-7.18 (2H, m), 5.14 (2H, s), 3.18 (2H, d, J = 6.8 Hz), 1.92 (1H, m), 0.95 (6H, d, J = 6.8 Hz).

Example 7(42)

Benzyl 2'-(4-amidinophenylcarbamoyl)-4'-methoxy-4-((1-methoxycarbonyl-2-methylpropyl)carbamoyl)-2-biphenylcarboxylate

[0156]



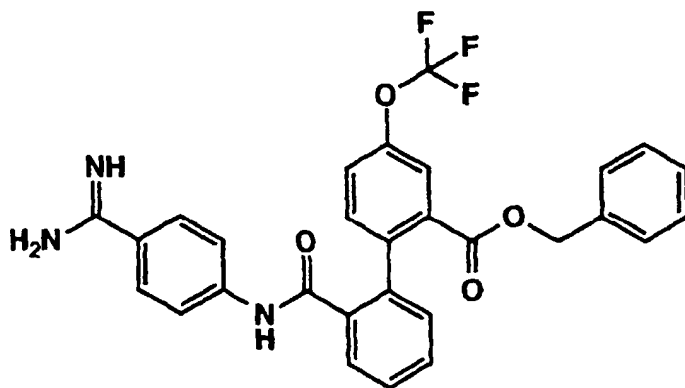
TLC : Rf 0.31 (Chloroform : Methanol : Water = 8 : 2 : 0.2) ;

NMR (CD₃OD) : δ 8.30 (1H, d, J = 1.8 Hz), 7.97 (1H, dd, J = 1.8, 8.0 Hz), 7.68 (2H, d, J = 9.2 Hz), 7.59 (2H, d, J = 9.2 Hz), 7.42 (1H, d, J = 8.0 Hz), 7.25-7.30 (3H, m), 7.14-7.20 (4H, m), 7.06 (1H, dd, J = 1.8, 8.0 Hz), 5.14 (2H, s), 4.47 (1H, d, J = 7.0 Hz), 3.90 (3H, s), 3.74 (3H, s), 2.25 (1H, m), 1.02 (3H, d, J = 7.0 Hz), 1.00 (3H, d, J = 7.0 Hz).

Example 7(43)

Benzyl 2'-(4-amidinophenylcarbamoyl)-4-trifluoromethoxy-2-biphenylcarboxylate

[0157]

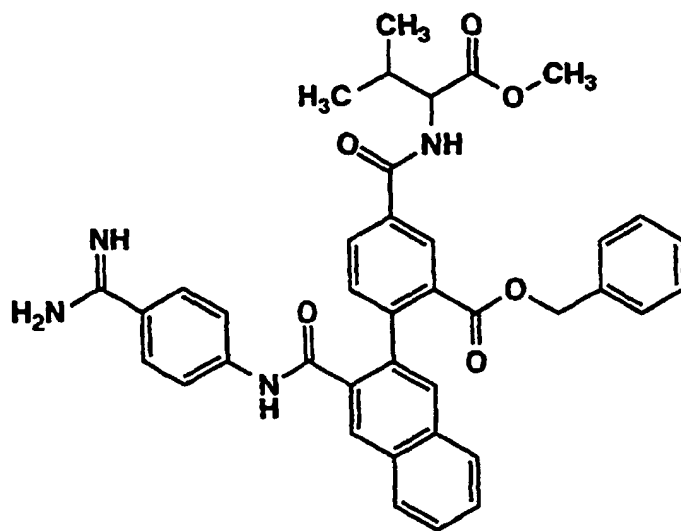


TLC : Rf 0.38 (Chloroform : Methanol : Water = 8 : 2 : 0.1) ;
 NMR (CD₃OD) : δ 7.73-7.11 (16H, m), 5.11 (2H, s).

Example 7(44)

Benzyl 2-(3-(4-amidinophenylcarbamoyl)naphthalen-2-yl)-5-((1-methoxycarbonyl-2-methylpropyl)carbanoyl)benzoate

[0158]



TLC : Rf 0.34 (Chloroform : Methanol : Water = 8 : 2 : 0.2) ;
 NMR (CD₃OD) : δ 8.39 (1H, d, J = 1.8 Hz), 8.21 (1H, s), 8.00-8.07 (2H, m), 7.88 (1H, m), 7.75 (1H, s), 7.71 (4H, s),
 7.62-7.66 (2H, m), 7.53 (1H, d, J = 7.8 Hz), 6.92-7.13 (5H, m), 5.06 (2H, s), 4.50 (1H, d, J = 7.0 Hz), 3.75 (3H, s),
 2.27 (1H, m), 1.04 (3H, d, J = 6.6 Hz), 1.02 (3H, d, J = 6.6 Hz).

Example 7(45)

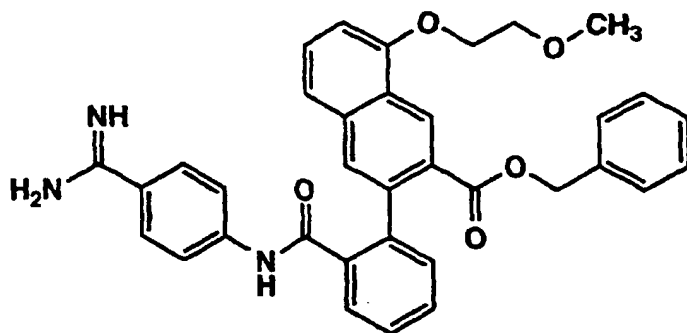
Benzyl 3-(2-(4-amidinophenylcarbamoyl)phenyl)-8-(2-methoxyethoxy)-2-naphthalenecarboxylate

5 [0159]

10

15

20



25 TLC : Rf 0.32 (Chloroform : Methanol : Water = 10 : 3 : 0.2) ;
 NMR (d_6 -DMSO) : δ 10.58 (1H, s), 9.09 (3H, br.s), 8.65 (1H, s), 7.79 (1H, s), 7.75-7.65 (5H, m), 7.65-7.4 (5H, m), 7.3-7.2 (3H, m), 7.2-7.0 (3H, m), 5.04 (2H, br.s), 4.4-4.2 (2H, m), 3.8-3.7 (2H, m), 3.32 (3H, s).

Example 7(46)

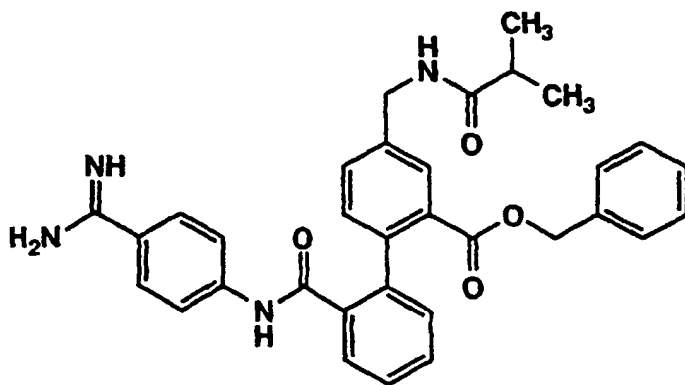
30 Benzyl 2'-(4-amidinophenylcarbamoyl)-4-((isopropylcarbonyl)aminomethyl)-2-biphenylcarboxylate

[0160]

35

40

45



50

55 TLC : Rf 0.32 (Chloroform : Methanol : Water = 8 : 2 : 0.1) ;
 NMR (CD_3OD) : δ 7.76-7.42 (9H, m), 7.30-7.14 (7H, m), 5.12 (2H, s), 4.38 (2H, s), 2.53-2.40 (1H, m), 1.09 (6H, d, $J = 6.8$ Hz).

Example 7(47)

Benzyl 2-(3-(4-amidinophenylcarbamoyl)naphthalen-2-yl)-5-((2-methylpropyl)carbamoyl)benzoate

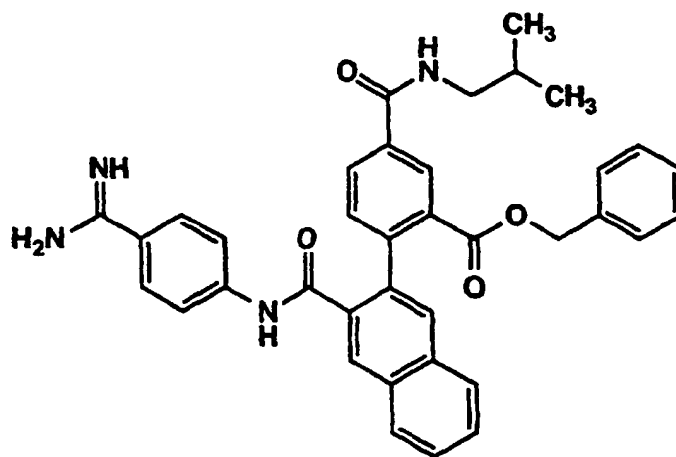
5 [0161]

10

15

20

25



30

TLC : Rf 0.35 (Chloroform : Methanol : Water = 8 : 2 : 0.2) ;

NMR (CD₃OD) : δ 8.38 (1H, d, J = 2.0 Hz), 8.22 (1H, s), 8.00-8.06 (2H, m), 7.90 (1H, m), 7.76 (1H, s), 7.71 (4H, s), 7.62-7.69 (3H, m), 7.53 (1H, d, J = 8.0 Hz), 6.91-7.13 (4H, m), 5.06 (2H, s), 3.21 (2H, d, J = 7.0 Hz), 1.94 (1H, m), 0.97 (6H, d, J = 6.6 Hz).

Example 7(48)

35

Benzyl 2'-(4-amidinophenylcarbamoyl)-4'-methoxy-4-((2-methylpropyl)carbamoyl)-2-biphenylcarboxylate

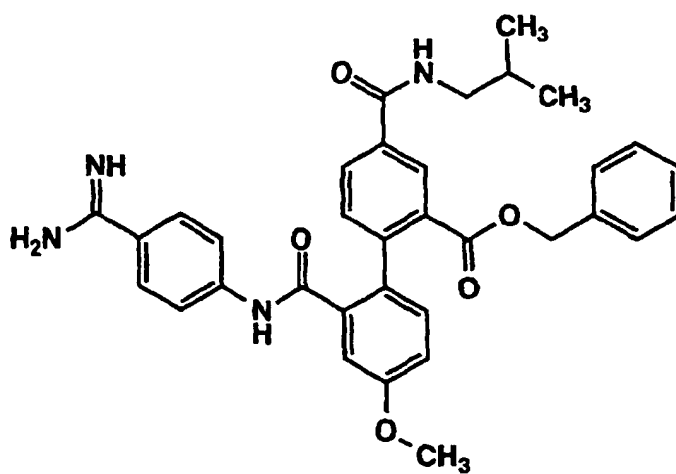
[0162]

40

45

50

55



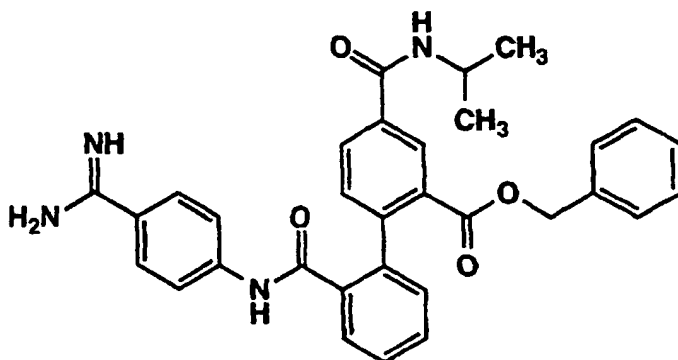
TLC : Rf 0.38 (Chloroform : Methanol : Water = 8 : 2 : 0.2) ;

NMR (CD₃OD) : δ 8.29 (1H, d, J = 2.0 Hz), 7.94 (1H, dd, J = 2.0, 8.0 Hz), 7.67 (2H, d, J = 9.2 Hz), 7.58 (2H, d, J = 9.2 Hz), 7.40 (1H, d, J = 8.0 Hz), 7.25-7.30 (3H, m), 7.15-7.19 (4H, m), 7.05 (1H, dd, J = 2.6, 8.8 Hz), 5.14 (2H, s), 3.89 (3H, s), 3.18 (2H, d, J = 7.0 Hz), 1.91 (1H, m), 0.95 (6H, d, J = 6.6 Hz).

Example 7(49)

Benzyl 2'-(4-amidinophenylcarbamoyl)-4-isopropylcarbamoyl-2-biphenylcarboxylate

[0163]



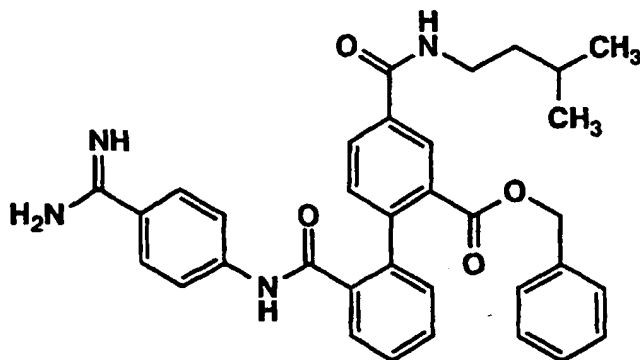
TLC : Rf 0.19 (Chloroform : Methanol : Water = 8 : 2 : 0.1) ;

NMR (CD₃OD) : δ 8.30 (1H, d, J = 1.8 Hz), 7.96 (1H, dd, J = 1.8, 7.6 Hz), 7.70-7.50 (7H, m), 7.41 (1H, d, J = 8.0 Hz), 7.29-7.26 (4H, m), 7.18-7.12 (2H, m), 5.14 (2H, s), 4.19 (1H, quintet, J = 6.6 Hz), 1.24 (6H, d, J = 6.6 Hz).

Example 7(50)

Benzyl 2'-(4-amidinophenylcarbamoyl)-4-((3-methylbutyl)carbamoyl)-2-biphenylcarboxylate

[0164]



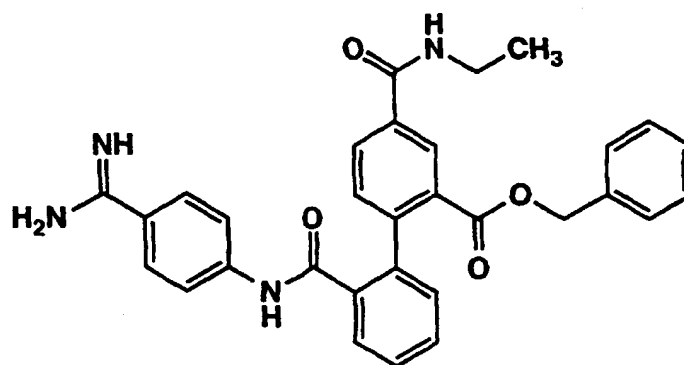
EP 1 078 917 A1

TLC : Rf 0.34 (Chloroform : Methanol : Water = 8 : 2 : 0.1) ;

NMR (CD₃OD) : δ 8.31 (1H, d, J = 1.8 Hz), 7.96 (1H, dd, J = 1.8, 8.0 Hz), 7.69-7.50 (7H, m), 7.42 (1H, d, J = 8.0 Hz), 7.29-7.26 (4H, m), 7.18-7.12 (2H, m), 5.13 (2H, s), 3.43-3.29 (2H, m), 1.75-1.60 (1H, m), 1.60-1.45 (2H, m), 0.95 (6H, d, J = 6.6 Hz).

Example 7(51)

Benzyl 2'-(4-amidinophenylcarbamoyl)-4-ethylcarbamoyl-2-biphenylcarboxylate

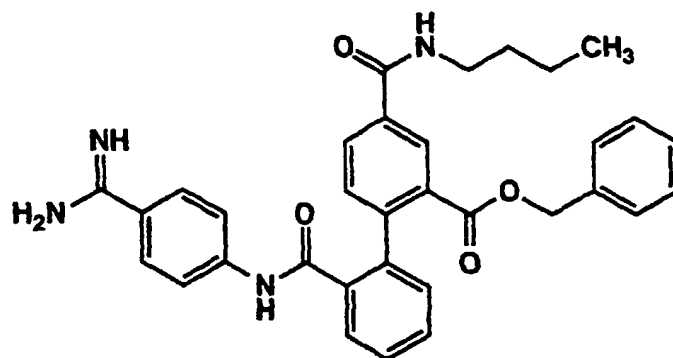


TLC : Rf 0.29 (Chloroform : Methanol : Water = 8 : 2 : 0.1) ;

NMR (CD₃OD) : δ 8.32 (1H, d, J = 1.8 Hz), 7.97 (1H, dd, J = 1.8, 8.0 Hz), 7.69-7.50 (7H, m), 7.42 (1H, d, J = 8.0 Hz), 7.29-7.26 (4H, m), 7.17-7.15 (2H, m), 5.13 (2H, s), 3.45-3.35 (2H, m), 1.21 (3H, t, J = 7.4 Hz).

Example 7(52)

Benzyl 2'-(4-amidinophenylcarbamoyl)-4-butylcarbamoyl-2-biphenylcarboxylate



TLC : Rf 0.36 (Chloroform : Methanol : Water = 8 : 2 : 0.1) ;

NMR (CD₃OD) : δ 8.31 (1H, d, J = 1.8 Hz), 7.97 (1H, dd, J = 1.8, 8.0 Hz), 7.70-7.50 (7H, m), 7.42 (1H, d, J = 8.0 Hz), 7.29-7.25 (4H, m), 7.18-7.12 (2H, m), 5.13 (2H, s), 3.40-3.32 (2H, m), 1.65-1.30 (4H, m), 0.96 (3H, t, J = 7.4 Hz).

5 Example 7(53)

Benzyl 2'-(4-amidinophenylcarbamoyl)-4'-methyl-4-((2-methylpropyl)carbamoyl)-2-biphenylcarboxylate

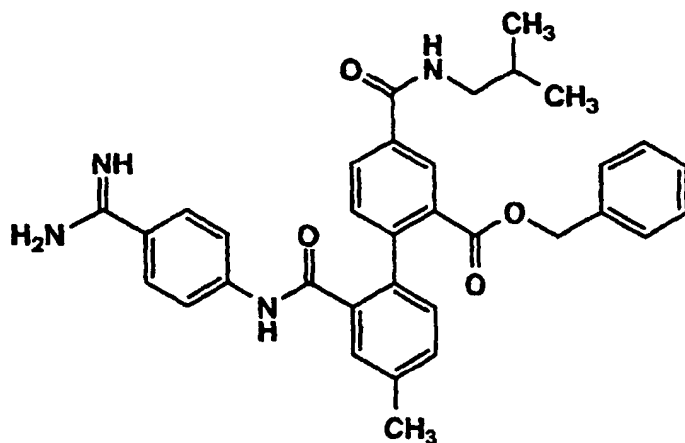
[0167]

10

15

20

25



30

TLC : Rf 0.33 (Chloroform : Methanol : Water = 8 : 2 : 0.2) ;

NMR (CD₃OD) : δ 8.31 (1H, d, J = 1.8 Hz), 7.95 (1H, dd, J = 1.8, 8.0 Hz), 7.67 (2H, d, J = 8.8 Hz), 7.59 (2H, d, J = 8.8 Hz), 7.47 (1H, m), 7.39 (1H, d, J = 8.0 Hz), 7.35 (1H, m), 7.25-7.31 (3H, m), 7.11-7.17 (3H, m), 5.13 (2H, s), 3.18 (2H, d, J = 6.8 Hz), 2.46 (3H, s), 1.91 (1H, m), 0.95 (6H, d, J = 6.6 Hz).

35

Example 7(54)

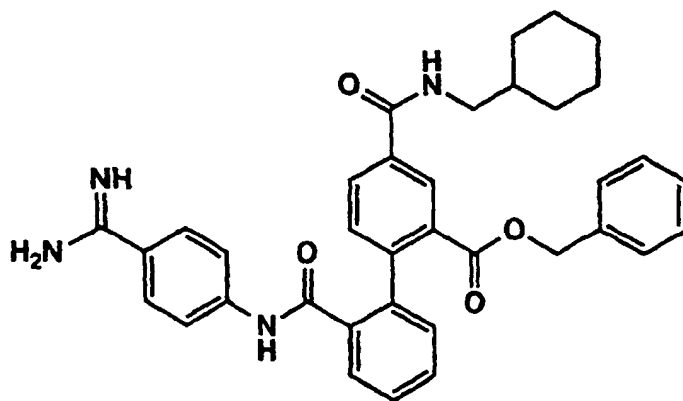
Benzyl 2'-(4-amidinophenylcarbamoyl)-4-((cyclohexylmethyl)carbamoyl)-2-biphenylcarboxylate

40 [0168]

45

50

55



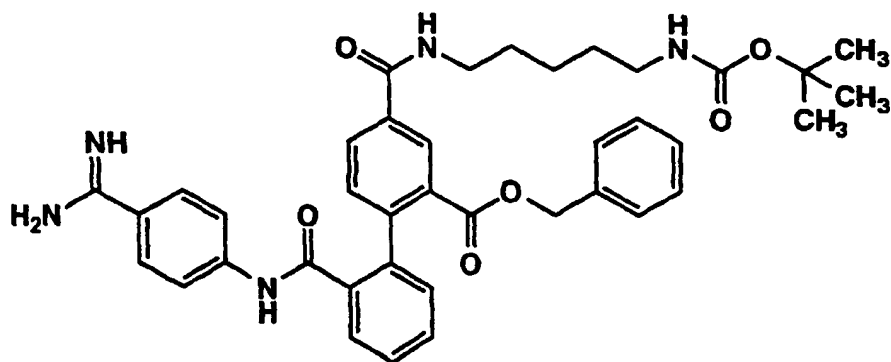
TLC : Rf 0.38 (Chloroform : Methanol : Water = 8 : 2 : 0.1) ;

NMR (CD₃OD) : δ 8.31 (1H, d, J = 1.8 Hz), 7.97 (1H, dd, J = 1.8, 8.0 Hz), 7.69-7.50 (7H, m), 7.42 (1H, d, J = 8.0 Hz), 7.29-7.26 (4H, m), 7.18-7.15 (2H, m), 5.13 (2H, s), 3.20 (2H, d, J = 7.0 Hz), 1.85-1.40 (6H, m), 1.40-0.90 (5H, m).

Example 7(55)

Benzy 2'-(4-amidinophenylcarbamoyl)-4-((5-(t-butoxycarbonylamino) pentyl)carbamoyl)-2-biphenylcarboxylate

[0169]



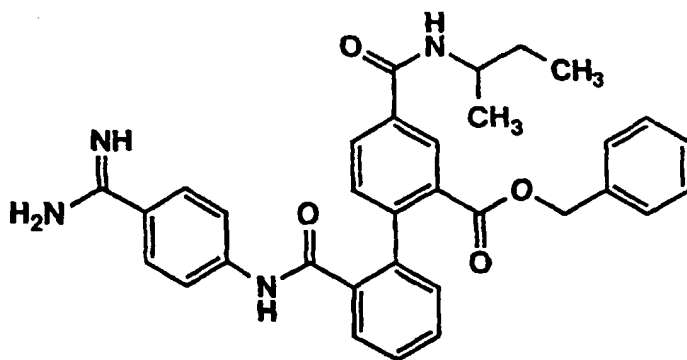
TLC : Rf 0.43 (Chloroform : Methanol : Water = 8 : 2 : 0.1) ;

NMR (CD₃OD) : δ 8.32 (1H, d, J = 1.8 Hz), 7.97 (1H, dd, J = 1.8, 8.0 Hz), 7.70-7.50 (7H, m), 7.42 (1H, d, J = 8.0 Hz), 7.29-7.25 (4H, m), 7.18-7.13 (2H, m), 5.13 (2H, s), 3.40-3.32 (2H, m), 3.03 (2H, t, J = 6.6 Hz), 1.70-1.30 (6H, m), 1.41 (9H, s).

Example 7(56)

Benzy 2'-(4-amidinophenylcarbamoyl)-4-((1-methylpropyl)carbamoyl)-2-biphenylcarboxylate

[0170]



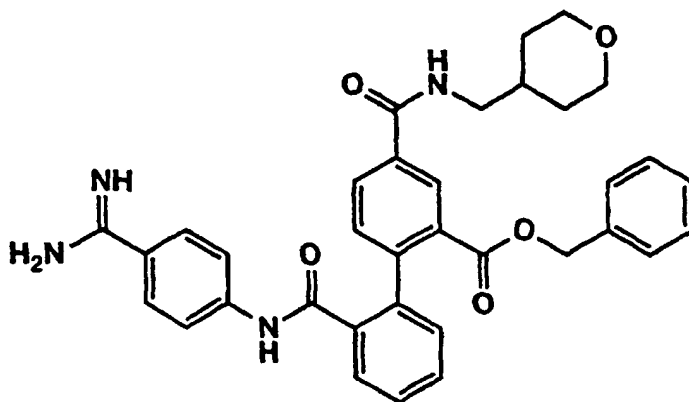
TLC : Rf 0.33 (Chloroform : Methanol : Water = 8 : 2 : 0.1) ;

NMR (CD₃OD) : δ 8.31 (1H, d, J = 2.0 Hz), 7.97 (1H, dd, J = 2.0, 8.0 Hz), 7.70-7.50 (7H, m), 7.42 (1H, d, J = 8.0 Hz), 7.29-7.25 (4H, m), 7.18-7.13 (2H, m), 4.01 (1H, sextet, J = 6.6 Hz), 1.66-1.51 (2H, m), 1.21 (3H, d, J = 6.6 Hz), 0.94 (3H, t, J = 7.2 Hz).

Example 7(57)

Benzy 2'-(4-amidinophenylcarbamoyl)-4-((tetrahydropyran-4-ylmethyl) carbamoyl)-2-biphenylcarboxylate

[0171]



TLC : Rf 0.48 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (CD₃OD) : δ 8.31 (1H, d, J = 2.0 Hz), 7.97 (1H, dd, J = 8.0 Hz, 2.0 Hz), 7.69-7.65 (3H, m), 7.60 (2H, d, J = 9.0 Hz), 7.57-7.47 (2H, m), 7.42 (1H, d, J = 8.0 Hz), 7.29-7.23 (4H, m), 7.17-7.12 (2H, m), 5.12 (2H, brs), 3.93 (2H, dd, J = 11 Hz, 2.5 Hz), 3.38 (2H, td, J = 11 Hz, 2.0 Hz), 3.26 (2H, d, J = 7.0 Hz), 1.96-1.80 (1H, m), 1.65 (2H, dd, J = 13 Hz, 1.0 Hz), 1.40-1.24 (2H, m).

Example 7(58)

Benzyl 2'-(4-amidinophenylcarbamoyl)-4-((2-benzylloxycarbonyloxypropyl) carbamoyl)-2-biphenylcarboxylate

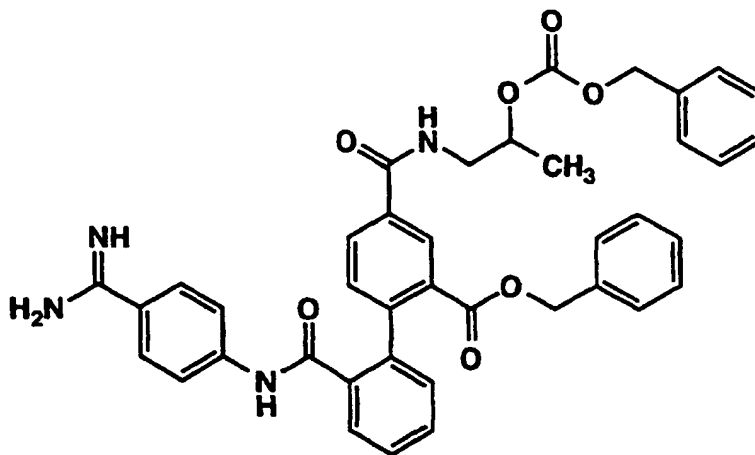
5 [0172]

10

15

20

25



30

TLC : Rf 0.52 (Chloroform : Methanol : Water = 8 : 2 : 0.1) ;

NMR (CD₃OD) : δ 8.31 (1H, d, J = 1.8 Hz), 7.92 (1H, dd, J = 1.8, 8.0 Hz), 7.68-7.51 (7H, m), 7.41 (1H, d, J = 8.2 Hz), 7.28-7.25 (9H, m), 7.17-7.14 (2H, m), 5.12 (2H, s), 5.07 (2H, s), 5.07-4.90 (1H, m), 3.61 (1H, dd, J = 4.0, 14.0 Hz), 3.47 (1H, dd, J = 7.4, 14.0 Hz), 1.30 (3H, d, J = 6.4 Hz).

Example 7(59)

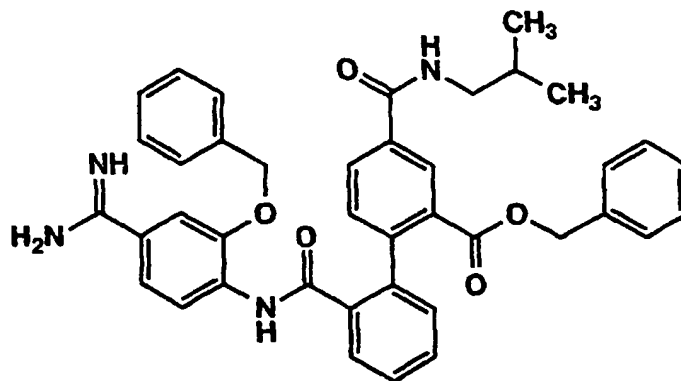
35 Benzyl 2'-(4-amidino-2-benzyloxyphenylcarbamoyl)-4-((2-methylpropyl) carbamoyl)-2-biphenylcarboxylate

[0173]

40

45

50



55

TLC : Rf 0.71 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

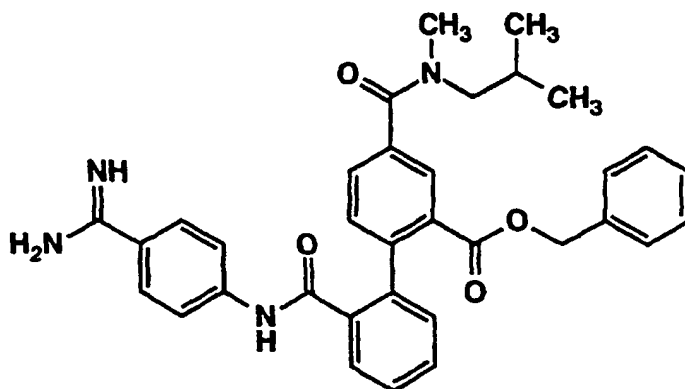
NMR (CD₃OD) : δ 8.43 (1H, d, J = 8.5 Hz), 8.24 (1H, d, J = 2.0 Hz), 7.86 (1H, dd, J = 8.0 Hz, 2.0 Hz), 7.69-7.65 (1H, m), 7.51-7.42 (2H, m), 7.38-7.29 (5H, m), 7.27 (1H, d, J = 1.5 Hz), 7.25-7.16 (5H, m), 7.13-7.09 (1H, m), 7.02-

6.98 (2H, m), 5.06 (1H, d, J = 12 Hz), 5.01 (1H, d, J = 12 Hz), 4.94 (1H, d, J = 12 Hz), 4.86 (1H, d, J = 12 Hz), 3.18 (2H, d, J = 7.0 Hz), 1.98-1.84 (1H, m), 0.95 (6H, d, J = 6.5 Hz).

Example 7(60)

Benzyl 2'-(4-amidinophenylcarbamoyl)-4-(N-methyl-N-(2-methylpropyl)carbamoyl)-2-biphenylcarboxylate

[0174]



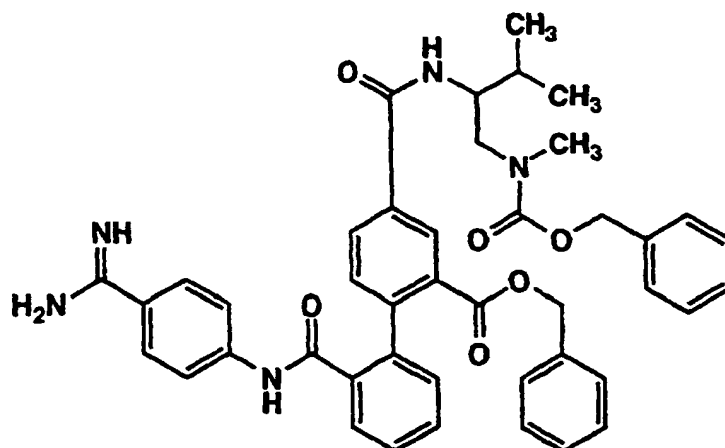
TLC : Rf 0.43 (Chloroform : Methanol : Water = 8 : 2 : 0.1) ;

NMR (CD₃OD) : δ 7.87 (1H, br s), 7.71-7.41 (9H, m), 7.31-7.26 (4H, m), 7.15-7.13 (2H, m), 5.13 (2H, s), 3.40-3.31 (2H, m, each of rotamers), 3.30-3.05 (2H, m, each of rotamers), 3.05 (3H, s, each of rotamers), 2.89 (3H, s, each of rotamers), 2.20-1.80 (1H, m), 0.98 (3H, d, J = 6.6 Hz, each of rotamers), 0.65 (3H, d, J = 6.6 Hz, each of rotamers).

Example 7(61)

Benzyl 2'-(4-amidinophenylcarbamoyl)-4-((2-methyl-1-(N-methyl-N-benzyl oxycarbonylaminoethyl)propyl)carbamoyl)-2-biphenylcarboxylate

[0175]



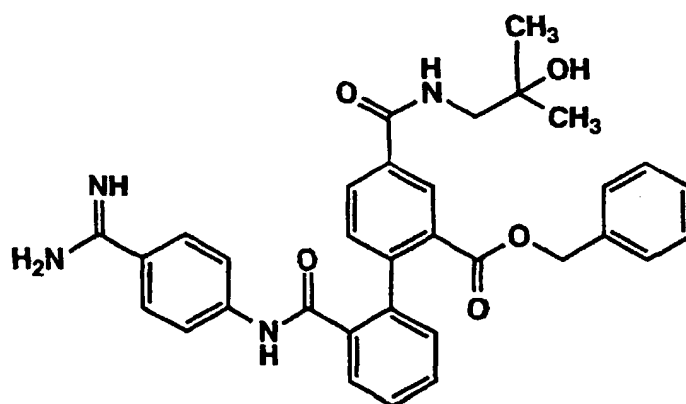
TLC : Rf 0.54 (Chloroform : Methanol : Water = 10 : 3 : 0.2) ;

NMR (d_6 -DMSO) : δ 10.68 (1H, br.s), 9.4-8.8 (3H, br), 8.5-8.2 (1H, br), 8.24 (1H, br.s), 8.1-7.9 (1H, br), 7.8-7.6 (5H, m), 7.56 (2H, m), 7.40 (1H, d, J = 8.2 Hz), 7.4-7.1 (9H, m), 7.1-7.0 (2H, m), 5.03 (2H, s), 4.97 (2H, s), 4.2-4.0 (1H, br), 3.7-3.2 (2H, m), 2.9-2.7 (3H, m), 1.75 (1H, m), 1.0-0.8 (6H, m).

Example 7(62)

Benzyl 2'-(4-amidinophenyl)carbamoyl)-4-((2-hydroxy-2-methylpropyl)carbamoyl)-2-biphenylcarboxylate

[0176]



TLC : Rf 0.40 (Chloroform : Methanol : Water = 8 : 2 : 0.1) ;

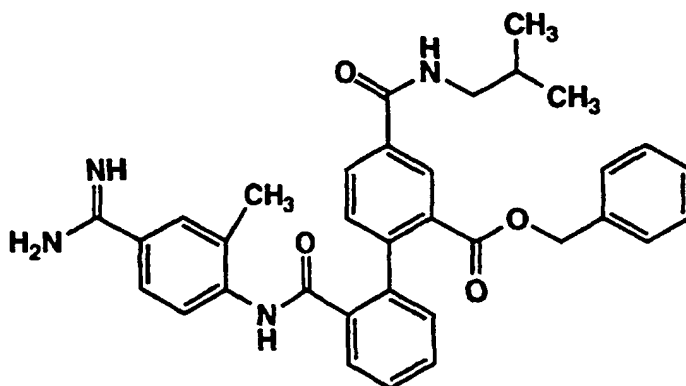
EP 1 078 917 A1

NMR (CD₃OD) : δ 8.35 (1H, d, J = 2.2 Hz), 8.01 (1H, dd, J = 2.2, 8.0 Hz), 7.70-7.61 (5H, m), 7.55-7.50 (2H, m), 7.44 (1H, d, J = 8.0 Hz), 7.30-7.20 (4H, m), 7.18-7.13 (2H, m), 5.13 (2H, s), 3.40 (2H, s), 1.22 (6H, s).

Example 7(63)

Benzyl 2'-(4-amidino-2-methylphenylcarbamoyl)-4-((2-methylpropyl) carbamoyl)-2-biphenylcarboxylate

[0177]



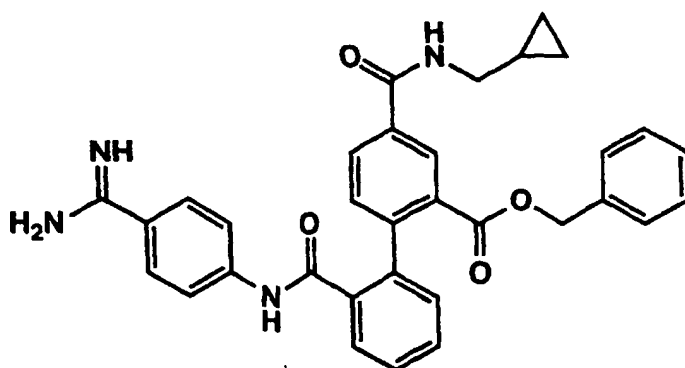
TLC : Rf 0.61 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (CD₃OD) : δ 8.35 (1H, d, J = 2.0 Hz), 7.99 (1H, dd, J = 8.0 Hz, 2.0 Hz), 7.76-7.70 (1H, m), 7.69 (1H, d, J = 8.0 Hz), 7.58-7.48 (4H, m), 7.45 (1H, d, J = 8.0 Hz), 7.30-7.21 (4H, m), 7.21-7.10 (2H, m), 5.14 (2H, s), 3.19 (2H, d, J = 7.0 Hz), 1.95 (3H, s), 2.02-1.81 (1H, m), 0.95 (6H, d, J = 6.5 Hz).

Example 7(64)

Benzyl 2'-(4-amidinophenylcarbamoyl)-4-((cyclopropylmethyl)carbamoyl)-2-biphenylcarboxylate

[0178]



TLC : Rf 0.27 (Chloroform : Methanol : Water = 8 : 2 : 0.2) ;

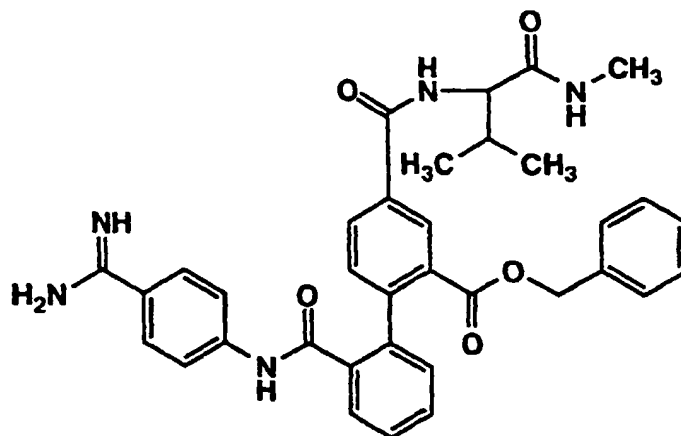
NMR (CD₃OD) : δ 8.34 (1H, d, J = 2.0 Hz), 7.98 (1H, dd, J = 2.0, 8.0 Hz), 7.50-7.70 (7H, m), 7.42 (1H, d, J = 8.0 Hz), 7.25-7.30 (4H, m), 7.14-7.19 (2H, m), 5.14 (2H, s), 3.23 (2H, d, J = 7.0 Hz), 1.09 (1H, m), 0.47-0.56 (2H, m),

0.23-0.30 (2H, m).

Example 7(65)

5 Benzyl 2'-(4-amidinophenylcarbamoyl)-4-((1-(methylcarbamoyl)-2-methylpropyl)carbamoyl)-2-biphenylcarboxylate

[0179]



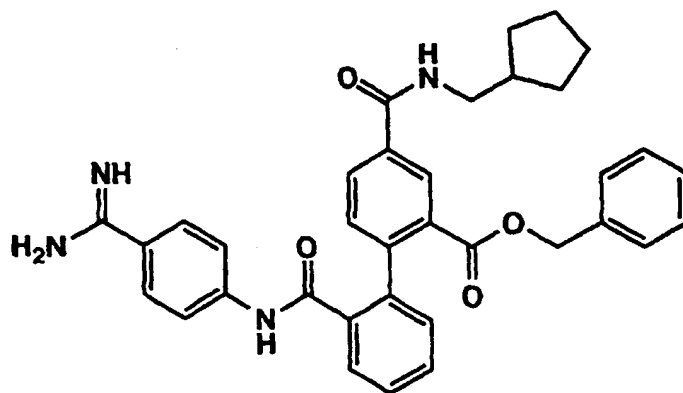
TLC : Rf 0.36 (Chloroform : Methanol : Water = 8 : 2 : 0.1) ;

30 NMR (CD₃OD) : δ 8.33 (1H, d, J = 1.5 Hz), 8.01 (1H, dd, J = 1.5, 7.8 Hz), 7.68-7.65 (4H, m), 7.61-7.58 (2H, m), 7.53-7.50 (2H, m), 7.44 (1H, d, J = 7.8 Hz), 7.28-7.26 (3H, m), 7.17-7.14 (2H, m), 5.13 (2H, s), 4.27 (1H, d, J = 8.1 Hz), 2.75 (3H, s), 2.14 (1H, sextet, J = 8.1 Hz), 1.01-0.97 (6H, m).

Example 7(66)

35 Benzyl 2'-(4-amidinophenylcarbamoyl)-4-((cyclopentylmethyl)carbamoyl)-2-biphenylcarboxylate

[0180]



TLC : Rf 0.30 (Chloroform : Methanol : Water = 8 : 2 : 0.2) ;

55 NMR (CD₃OD) : δ 8.32 (1H, d, J = 2.0 Hz), 7.96 (1H, dd, J = 2.0, 8.0 Hz), 7.67 (2H, d, J = 8.4 Hz), 7.59 (2H, d, J =

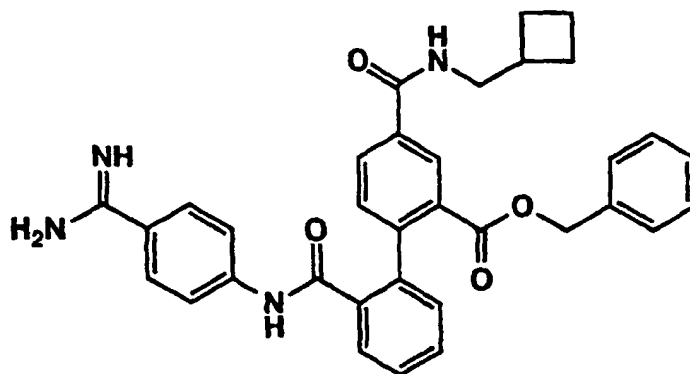
EP 1 078 917 A1

8.4 Hz), 7.50-7.55 (2H, m), 7.41 (1H, d, J = 8.0 Hz), 7.25-7.29 (4H, m), 7.13-7.18 (3H, m), 5.14 (2H, s), 3.29 (2H, d, J = 6.8 Hz), 2.21 (1H, m), 1.56-1.79 (6H, m), 1.27-1.31 (2H, m).

Example 7(67)

Benzy 2'-(4-amidinophenylcarbamoyl)-4-((cyclobutylmethyl)carbamoyl)-2-biphenylcarboxylate

[0181]



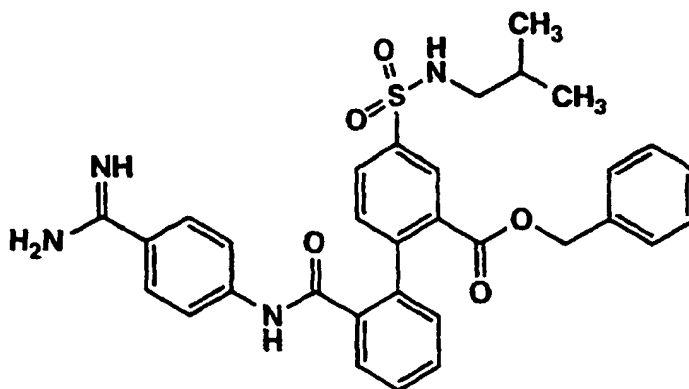
TLC : Rf 0.31 (Chloroform : Methanol : Water = 8 : 2 : 0.2) ;

NMR (CD₃OD) : δ 8.31 (1H, d, J = 2.0 Hz), 7.95 (1H, dd, J = 2.0, 8.0 Hz), 7.67 (2H, d, J = 9.2 Hz), 7.59 (2H, d, J = 9.2 Hz), 7.49-7.54 (2H, m), 7.41 (1H, d, J = 8.0 Hz), 7.24-7.29 (4H, m), 7.13-7.17 (3H, m), 5.13 (2H, s), 3.39 (2H, d, J = 7.0 Hz), 2.61 (1H, m), 1.76-2.11 (6H, m).

Example 7(68)

Benzy 2'-(4-amidinophenylcarbamoyl)-4-((2-methylpropyl)sulfamoyl)-2-biphenylcarboxylate

[0182]



TLC : Rf 0.43 (Chloroform : Methanol : Water = 8 : 2 : 0.1) ;

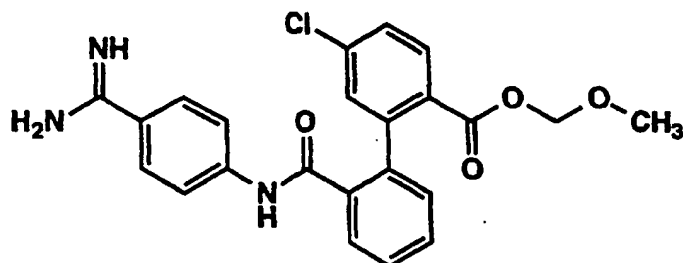
NMR (CD₃OD) : δ 8.30 (1H, d, J = 1.5 Hz), 7.91 (1H, d, J = 7.5 Hz), 7.65-7.60 (5H, m), 7.60-7.50 (3H, m), 7.30-

7.20 (4H, m), 7.20-7.10 (2H, m), 5.12 (2H, s), 2.63 (2H, d, J = 6.6 Hz), 1.70-1.60 (1H, m), 0.83 (6H, d, J = 6.6 Hz).

Example 7(69)

5 Methoxymethyl 2'-(4-amidinophenylcarbamoyl)-5-chloro-2-biphenylcarboxylate

[0183]

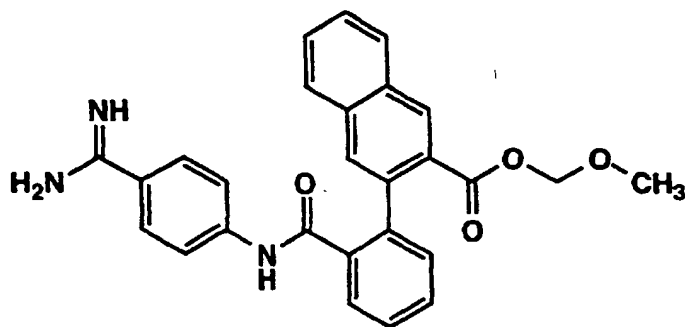


TLC : Rf 0.55 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1).

Example 7(70)

Methoxymethyl 3-(2-(4-amidinophenylcarbamoyl)phenyl)-2-naphthalene carboxylate

[0184]



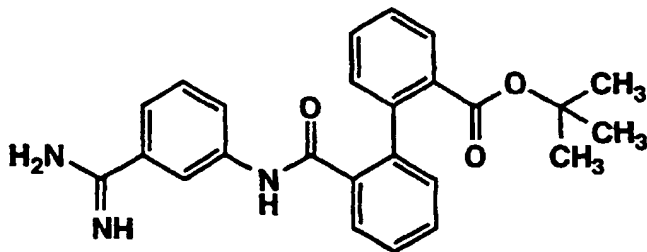
TLC : Rf 0.46 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d₆-DMSO) : δ 10.56 (1H, s), 9.2-8.9 (3H, s), 8.50 (1H, s), 8.12 (1H, d, J = 7.0 Hz), 7.97 (1H, d, J = 7.0 Hz), 7.83 (1H, s), 7.8-7.4 (10H, m), 5.16 (2H, br), 3.18 (3H, s).

Example 7(71)

t-Butyl 2'-(3-amidinophenylcarbamoyl)-2-biphenylcarboxylate

[0185]



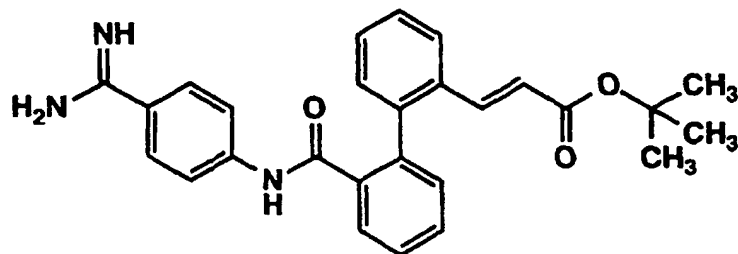
TLC : Rf 0.39 (Chloroform : Methanol : Water = 8 : 2 : 0.2) ;

NMR (CD₃OD) : δ 8.07 (1H, s), 7.81 (1H, dd, J = 1.6, 7.8 Hz), 7.73 (1H, m), 7.50-7.58 (2H, m), 7.44-7.50 (3H, m), 7.36-7.41 (2H, m), 7.23-7.28 (2H, m), 1.32 (9H, s).

Example 7(72)

t-Butyl 2-(2-(4-amidinophenylcarbamoyl)phenyl)cinnamate

[0186]



TLC : Rf 0.43 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

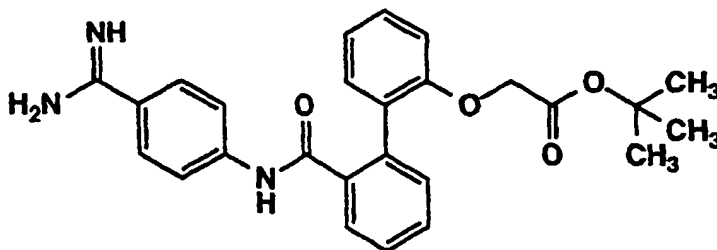
NMR (CD₃OD) : δ 7.76-7.30 (13H, m), 6.28 (1H, d, J = 16 Hz), 1.43 (9H, s).

Example 7(73)

t-Butyl 2'-(4-amidinophenylcarbamoyl)biphenyl-2-yloxyacetate

5 [0187]

10



15

20

TLC : Rf 0.52 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

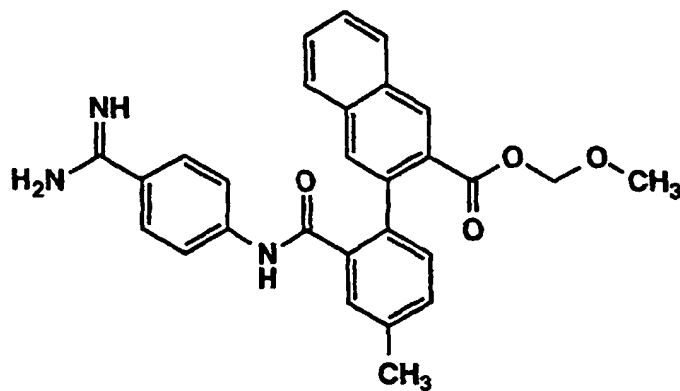
NMR (CD₃OD) : δ 7.75-7.43 (8H, m), 7.33-7.21 (2H, m), 7.01 (1H, td, J = 8.0 Hz, 1.0 Hz), 6.84 (1H, d, J = 8.0 Hz), 4.47 (2H, s), 1.40 (9H, s).

25 Example 7(74)

Methoxymethyl 3-(2-(4-amidinophenylcarbamoyl)-4-methylphenyl)-2-naphthalenecarboxylate

30 [0188]

35



40

45

TLC : Rf 0.27 (Chloroform : Methanol = 4 : 1) ;

50

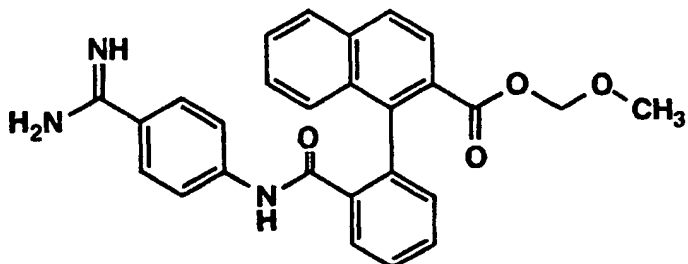
NMR (CDCl₃) : δ 9.38 (1H, s), 8.68 (2H, brs), 8.35 (3H, s), 7.80 (1H, dd, J = 7.0, 2.2 Hz), 7.7-7.6 (2H, m), 7.56 (2H, d, J = 8.4 Hz), 7.5-7.4 (2H, m), 7.37 (2H, d, J = 8.4 Hz), 7.22 (1H, dd, J = 7.6, 2.0 Hz), 7.05 (1H, d, J = 7.6 Hz), 5.37 (1H, d, J = 6.0 Hz), 5.30 (1H, d, J = 6.0 Hz), 3.35 (3H, s), 2.35 (3H, s).

55

Example 7(75)

Methoxymethyl 1-(2-(4-amidinophenylcarbamoyl)phenyl)-2-naphthalenecarboxylate

[0189]

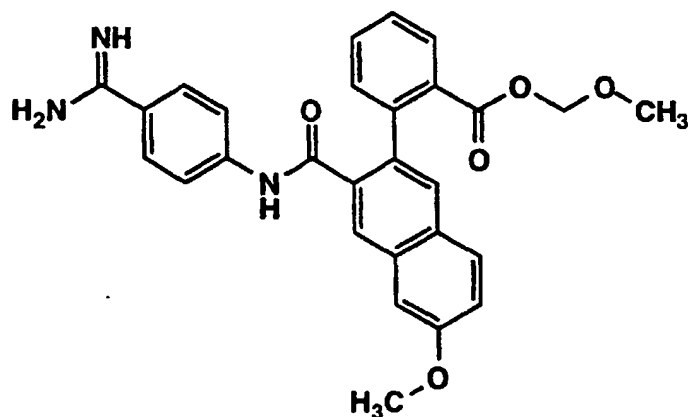


TLC : Rf 0.65 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1).

Example 7(76)

Methoxymethyl 2-(3-(4-amidinophenylcarbamoyl)-6-methoxynaphthalen-2-yl)benzoate

[0190]



TLC : Rf 0.51 (Chloroform : Methanol : Water = 10 : 3 : 0.2) ;

NMR (d₆-DMSO) : δ 10.74 (1H, br.s), 9.4-9.0 (3H, br), 8.16 (1H, s), 8.0-7.7 (3H, m), 7.79 (4H, like s), 7.63 (1H, m), 7.6-7.2 (4H, m), 5.07 (2H, br.s), 3.91 (3H, s), 3.03 (3H, s).

Example 7(77)

Methoxymethyl 3-(2-(4-amidinophenylcarbamoyl)-4-methoxyphenyl)-2-naphthalenecarboxylate

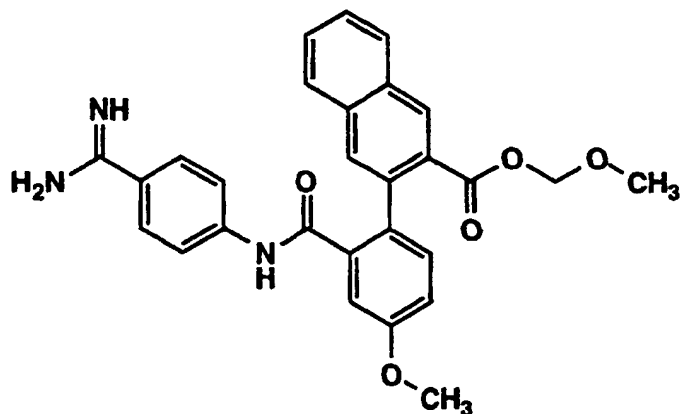
5 [0191]

10

15

20

25



30

TLC : Rf 0.55 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (CD₃OD) : δ 8.44 (1H, s), 7.96 (1H, dd, J = 7.0 Hz, 2.0 Hz), 7.87 (1H, dd, J = 7.0 Hz, 2.0 Hz), 7.79 (1H, s),
7.65-7.50 (6H, m), 7.31 (1H, d, J = 8.5 Hz), 7.25 (1H, d, J = 2.5 Hz), 7.15 (1H, dd, J = 8.5 Hz, 2.5 Hz), 5.32 (2H, s),
3.91 (3H, s), 3.36 (3H, s).

Example 7(78)

Methoxymethyl 3-(2-(4-amidinophenylcarbamoyl)-4-propoxyphenyl)-2-naphthalenecarboxylate

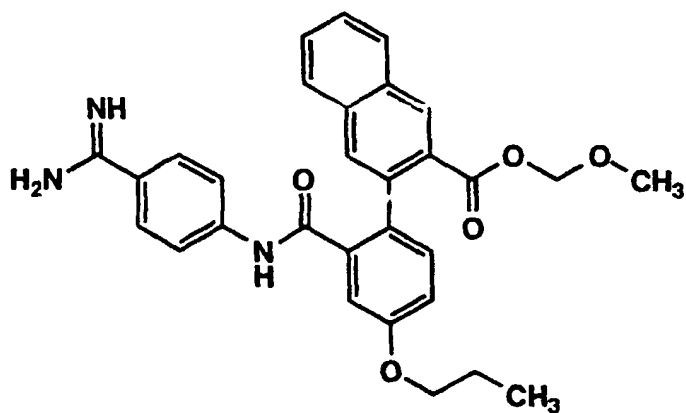
35

[0192]

40

45

50



55

TLC : Rf 0.65 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

EP 1 078 917 A1

NMR (CD₃OD) : δ 8.44 (1H, s), 7.96 (1H, dd, J = 7.0 Hz, 2.0 Hz), 7.87 (1H, dd, J = 7.0 Hz, 2.0 Hz), 7.79 (1H, s), 7.65-7.50 (6H, m), 7.30 (1H, d, J = 8.5 Hz), 7.24 (1H, d, J = 2.5 Hz), 7.14 (1H, dd, J = 8.5 Hz, 2.5 Hz), 5.32 (2H, s), 4.06 (2H, t, J = 7.0 Hz), 3.36 (3H, s), 1.86 (2H, sextet, J = 7.0 Hz), 1.09 (3H, t, J = 7.0 Hz).

5 Example 7(79)

Methoxymethyl 2-(3-(4-amidinophenylcarbamoyl)-7-methoxynaphthalen-2-yl)benzoate

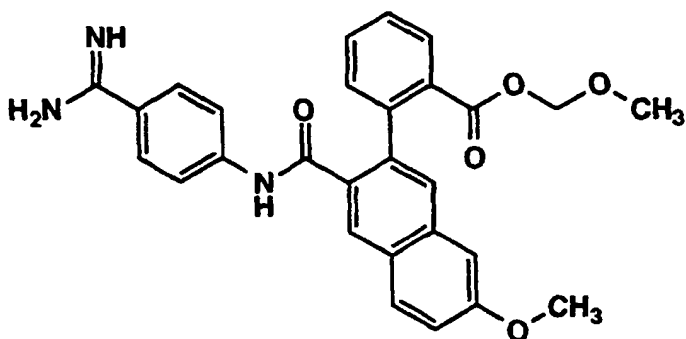
[0193]

10

15

20

25



TLC : Rf 0.71 (Chloroform : Methanol : Water = 10 : 3 : 0.2) .

30

Example 7(80)

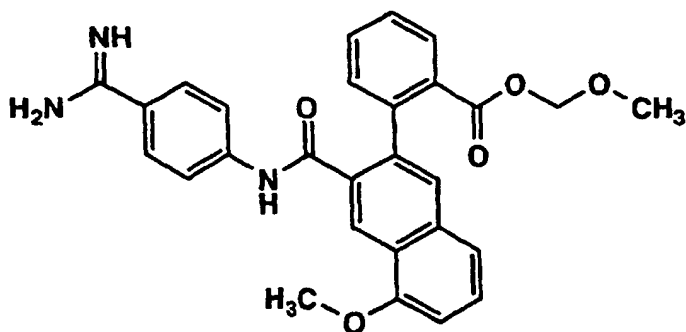
Methoxymethyl 2-(3-(4-amidinophenylcarbamoyl)-5-methoxynaphthalen-2-yl)benzoate

35 [0194]

40

45

50



TLC : Rf 0.54 (Chloroform : Methanol : Water = 10 : 3 : 0.2) ;

NMR (d₆-DMSO) : δ 10.80 (1H, s), 9.3-9.1 (3H, br), 8.44 (1H, s), 7.88 (1H, dd, J = 1.4, 7.4 Hz), 7.79 (4H, s), 7.7-7.3 (6H, m), 7.10 (1H, m), 5.07 (2H, br.s), 4.03 (3H, s), 3.03 (3H, s).

55

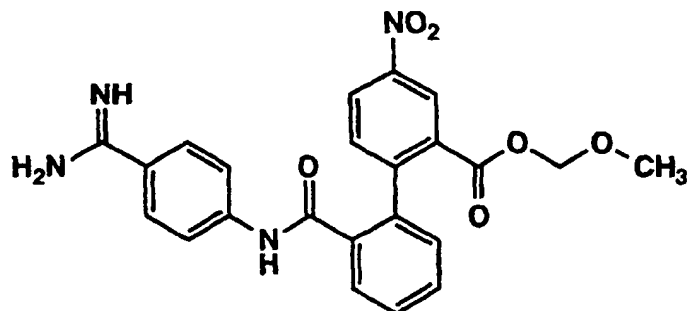
Example 7(81)

Methoxymethyl 2'-(4-amidinophenylcarbamoyl)-4-nitro-2-biphenylcarboxylate

5 [0195]

10

15



20

TLC : Rf 0.46 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (CD₃OD) : δ 8.71 (1H, d, J = 2.5 Hz), 8.41 (1H, dd, J = 8.5 Hz, 2.5 Hz), 7.81-7.52 (8H, m), 7.37 (1H, dd, J = 8.0 Hz, 1.5 Hz), 5.23 (2H, s), 3.22 (3H, s).

25

Example 7(82)

Methoxymethyl 2'-(4-amidinophenylcarbamoyl)-4-methylsulfonylamino-2-biphenylcarboxylate

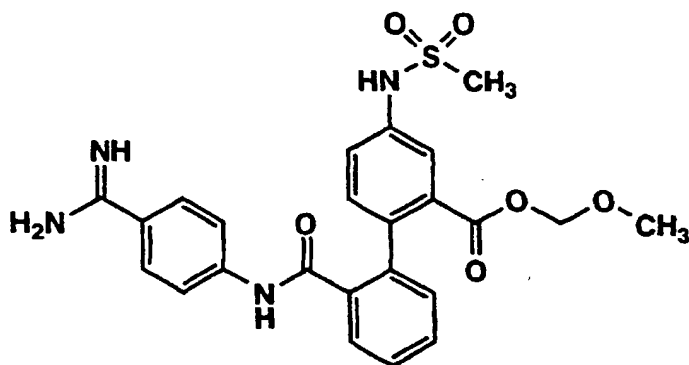
30

[0196]

35

40

45



50

TLC : Rf 0.44 (Chloroform : Methanol : Water = 7 : 3 : 0.3) ;

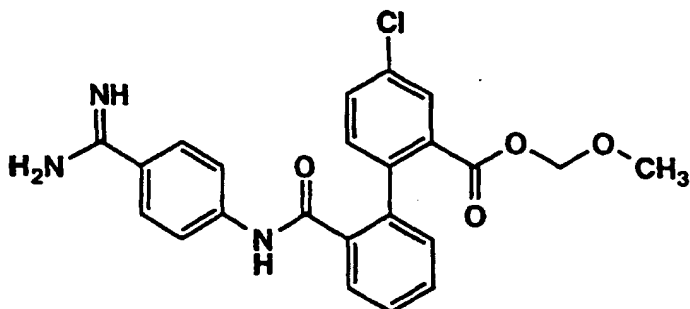
NMR (d₆-DMSO) : δ 10.49 (1H, brs), 10.2-9.8 (1H, broad), 9.3-8.9 (3H, broad), 7.80-7.22 (11H, m), 5.10 (2H, s), 3.12 (3H, s), 2.99 (3H, s).

55

Example 7(83)

Methoxymethyl 2'-(4-amidinophenylcarbamoyl)-4-chloro-2-biphenylcarboxylate

[0197]



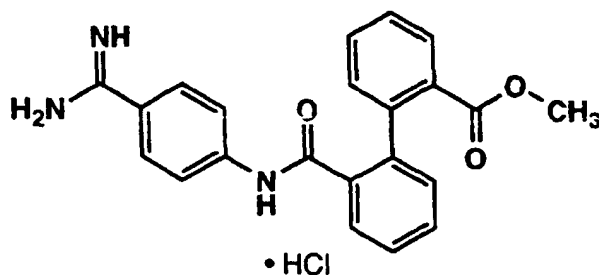
TLC : Rf 0.29 (Chloroform : Methanol : Water = 8 : 2 : 0.2) ;

NMR (CD₃OD) : δ 7.88 (1H, d, J = 2.0 Hz), 7.71 (4H, s), 7.68 (1H, m), 7.52-7.61 (3H, m), 7.30-7.35 (2H, m), 5.22 (2H, s), 3.24 (3H, s).

Example 7(84)

Methyl 2'-(4-amidinophenylcarbamoyl)-2-biphenylcarboxylate hydrochloride

[0198]



TLC : Rf 0.45 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d₆-DMSO) : δ 10.52 (1H, s), 9.29 (2H, brs), 9.12 (2H, brs), 7.82-7.25 (12H, m), 3.51 (3H, s).

Example 7(85)

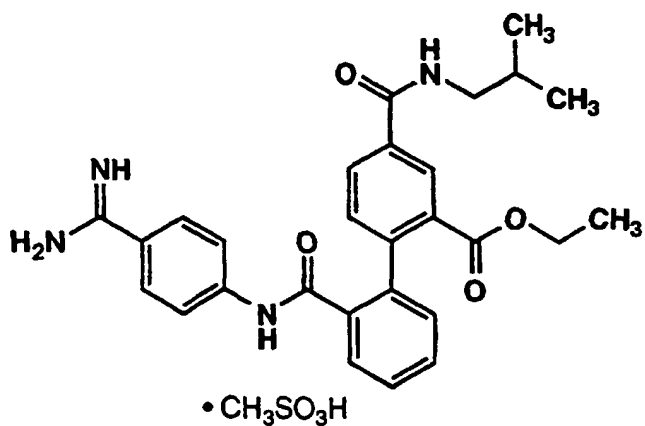
Ethyl 2'-(4-amidinophenylcarbamoyl)-4-((2-methylpropyl)carbamoyl)-2-biphenylcarboxylate methanesulfonate

5 [0199]

10

15

20



25

TLC : R_f 0.23 (Chloroform : Methanol : Water = 8 : 2 : 0.2) ;

NMR (d₆-DMSO) : δ 10.56 (1H, s), 9.15 (2H, s), 8.85 (2H, s), 8.66 (1H, br.t, J = 6.2 Hz), 8.24 (1H, d, J = 2.0 Hz), 8.03 (1H, dd, J = 2.0, 8.0 Hz), 7.74 (4H, s), 7.70 (1H, dd, J = 2.0, 8.0 Hz), 7.61 (1H, dt, J = 2.0, 8.0 Hz), 7.55 (1H, dt, J = 2.0, 8.0 Hz), 7.41 (1H, d, J = 8.0 Hz), 7.32 (1H, dd, J = 2.0, 8.0 Hz), 4.00 (2H, q, J = 6.6 Hz), 3.10 (2H, t, J = 6.2 Hz), 2.36 (3H, s), 1.86 (1H, m), 0.91 (3H, t, J = 6.6 Hz), 0.89 (6H, d, J = 6.4 Hz).

30

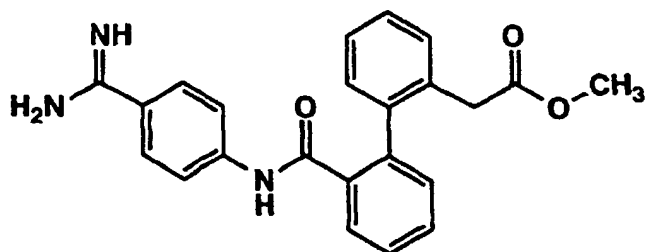
Example 7(86)

35 Methyl 2'-(4-amidinophenylcarbamoyl)biphenyl-2-ylacetate

[0200]

40

45



50

TLC : R_f 0.57 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

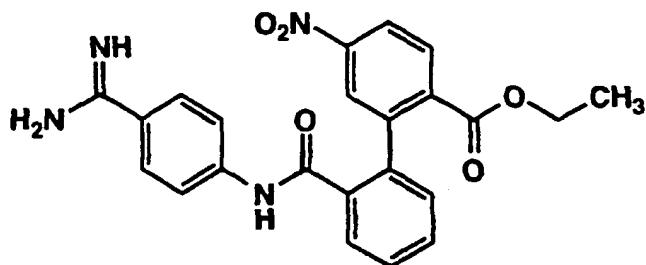
NMR (CD₃OD) : δ 7.76-7.64 (3H, m), 7.59-7.51 (4H, m), 7.42-7.35 (2H, m), 7.29-7.16 (3H, m), 4.09 (1H, d, J = 17 Hz), 3.74 (1H, d, J = 17 Hz), 3.52 (3H, s).

55

Example 7(87)

Ethyl 2'-(4-amidinophenylcarbamoyl)-5-nitro-2-biphenylcarboxylate

[0201]



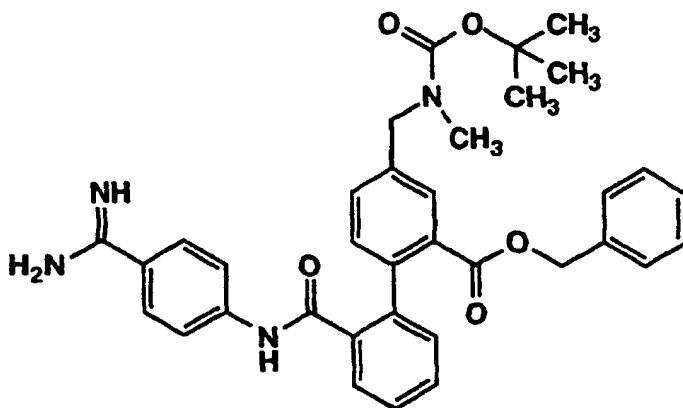
TLC : Rf 0.29 (Chloroform : Methanol : Water = 8 : 2 : 0.1) ;

NMR (CD₃OD) : δ 8.27 (1H, dd, J = 2.2, 8.4 Hz), 8.19 (1H, d, J = 2.2 Hz), 7.78-7.59 (7H, m), 7.38 (1H, dd, J = 1.8, 8.4 Hz), 4.11 (2H, q, J = 7.4 Hz), 1.02 (3H, t, J = 7.4 Hz).

Example 7(88)

Benzyl 2'-(4-amidinophenylcarbamoyl)-4-(N-methyl-N-(t-butoxycarbonyl)aminomethyl)-2-biphenylcarboxylate

[0202]



TLC : Rf 0.40 (Chloroform : Methanol : Water = 8 : 2 : 0.2) ;

NMR (CD₃OD) : δ 7.76 (1H, br.s), 7.62-7.68 (3H, m), 7.40-7.56 (5H, m), 7.27-7.33 (5H, m), 7.14-7.19 (2H, m), 5.13 (2H, s), 4.44 (2H, br.s), 2.73 (3H, br.s), 1.36 (9H, br.s).

Example 7(89)

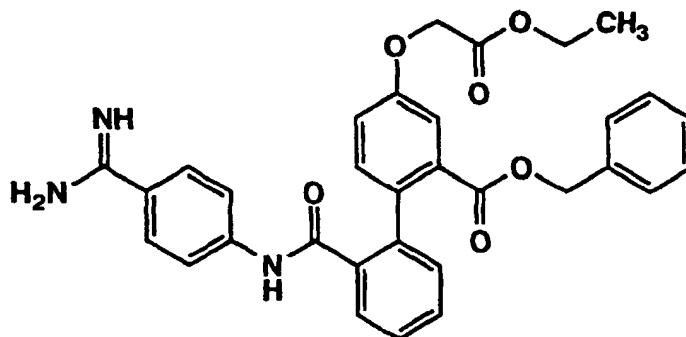
Benzyl 2'-(4-amidinophenylcarbamoyl)-4-ethoxycarbonylmethoxy-2-biphenylcarboxylate

5 [0203]

10

15

20



25

TLC : Rf 0.63 (Chloroform : Methanol : Water = 10 : 3 : 0.2) ;

NMR (d_6 -DMSO) : δ 10.51 (1H, s), 9.14 (3H, br.s), 7.9-7.6 (5H, m), 7.6-7.4 (2H, m), 7.4-7.1 (7H, m), 7.1-7.0 (2H, m), 5.01 (2H, s), 4.84 (2H, s), 4.13 (2H, q, J = 7.0 Hz), 1.16 (3H, t, J = 7.0 Hz).

Example 7(90)

30

Benzyl 2'-(4-amidinophenylcarbamoyl)-4-((1-methoxycarbonyl-2-methylpropyl)carbamoyl)-2-biphenylcarboxylate

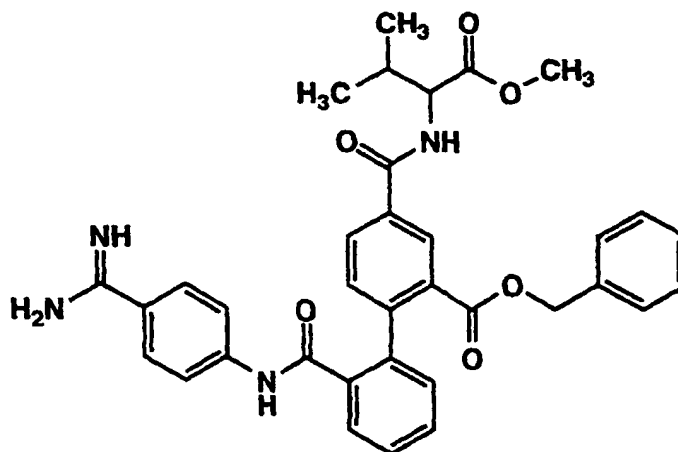
[0204]

35

40

45

50



55

TLC : Rf 0.41 (Chloroform : Methanol : Water = 8 : 2 : 0.2) ;

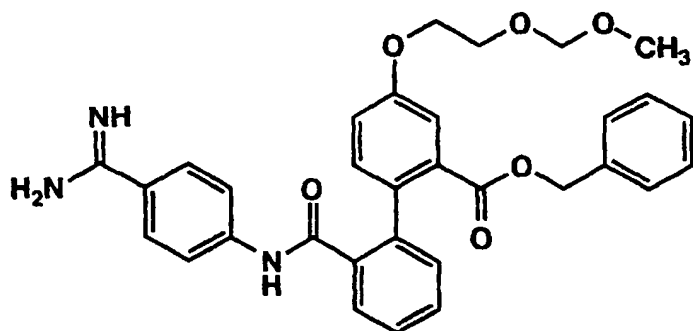
NMR (CD_3OD) : δ 8.34 (1H, d, J = 1.8 Hz), 8.00 (1H, dd, J = 1.8, 8.0 Hz), 7.59-7.71 (5H, m), 7.50-7.55 (2H, m), 7.43 (1H, d, J = 7.8 Hz), 7.26-7.29 (4H, m), 7.13-7.18 (2H, m), 5.13 (2H, s), 4.47 (1H, d, J = 6.8 Hz), 3.74 (3H, s), 2.25

(1H, m), 1.02 (3H, d, J = 7.0 Hz), 1.00 (3H, d, J = 7.0 Hz).

Example 7(91)

5 Benzyl 2'-(4-amidinophenylcarbamoyl)-4-(2-(methoxymethoxy)ethoxy)-2-biphenylcarboxylate

[0205]

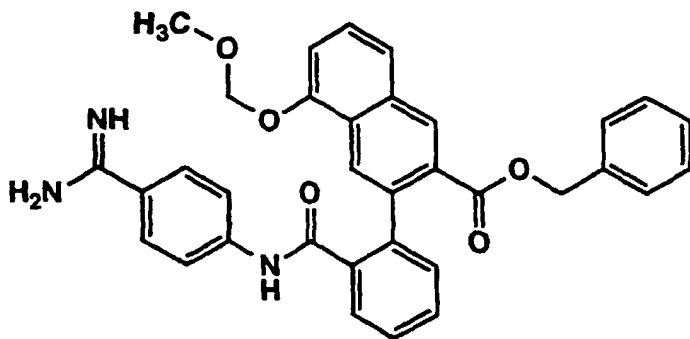


25 TLC : Rf 0.53 (Chloroform : Methanol : Water = 10 : 3 : 0.2) ;
NMR (d₆-DMSO) : δ 10.47 (1H, s), 9.12 (3H, br.s), 7.8-7.6 (4H, m), 7.7-7.5 (1H, m), 7.6-7.4 (2H, m), 7.3-7.1 (7H, m), 7.1-6.9 (2H, m), 5.01 (2H, s), 4.59 (2H, s), 4.2-4.0 (2H, m), 3.8-3.7 (2H, m), 3.24 (3H, s).

Example 7(92)

30 Benzyl 3-(2-(4-amidinophenylcarbamoyl)phenyl)-5-methoxymethoxy-2-naphthalenecarboxylate

[0206]



50 TLC : Rf 0.74 (Chloroform : Methanol : Water = 10 : 3 : 0.2) ;
NMR (d₆-DMSO) : δ 10.64 (1H, s), 9.11 (3H, br.s), 8.42 (1H, s), 8.06 (1H, s), 7.8-7.6 (6H, m), 7.6-7.4 (4H, m), 7.3-7.1 (4H, m), 7.2-7.0 (2H, m), 5.38 (2H, s), 5.08 (2H, s), 3.33 (3H, s).

55

Example 7(93)

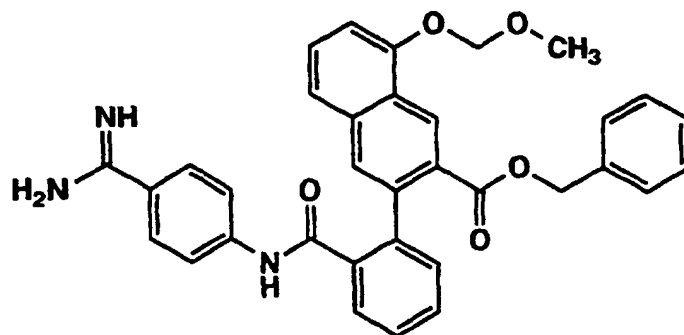
Benzyl 3-(2-(4-amidinophenylcarbamoyl)phenyl)-8-methoxymethoxy-2-naphthalenecarboxylate

5 [0207]

10

15

20



25 TLC : Rf 0.39 (Chloroform : Methanol : Water = 10 : 2 : 0.1) ;
 NMR (d₆-DMSO) : δ 10.59 (1H, s), 9.09 (3H, br.s), 8.66 (1H, s), 7.81 (1H, s), 7.71 (5H, like s), 7.7-7.5 (4H, m), 7.44 (1H, m), 7.3-7.1 (4H, m), 7.1-7.0 (2H, m), 5.44 (2H, s), 5.07 (2H, s), 3.43 (3H, s).

Example 7(94)

30 Benzyl 2'-(4-amidinophenylcarbamoyl)-4-(N-(t-butoxycarbonyl)-N-(2-methylpropyl)aminomethyl)-2-biphenylcarboxylate

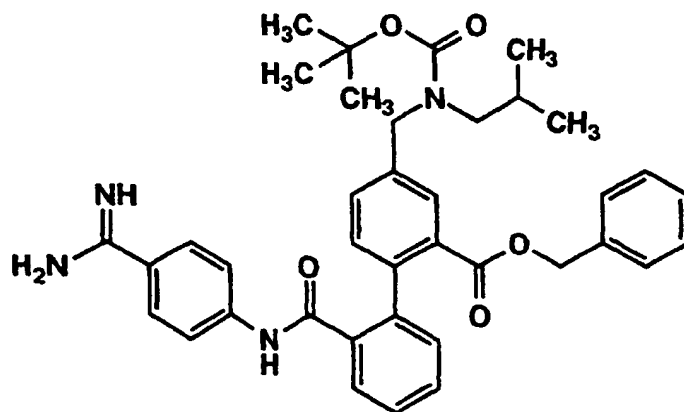
[0208]

35

40

45

50

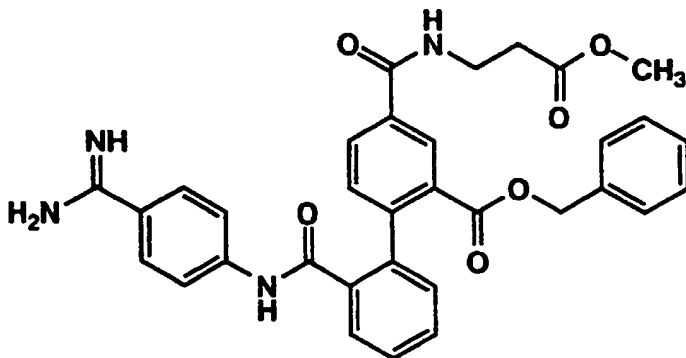


55 TLC : Rf 0.51 (Chloroform : Methanol : Water = 8 : 2 : 0.1) ;
 NMR (CD₃OD) : δ 7.76-7.39 (9H, m), 7.31-7.15 (7H, m), 5.13 (2H, s), 4.46 (2H, br s), 2.96 (2H, d, J = 7.2 Hz), 1.95-1.80 (1H, m), 1.43-1.30 (9H, m), 0.82 (6H, d, J = 6.6 Hz).

Example 7(95)

Benzyl 2'-(4-amidinophenylcarbamoyl)-4-((2-methoxycarbonylethyl)carbamoyl)-2-biphenylcarboxylate

[0209]



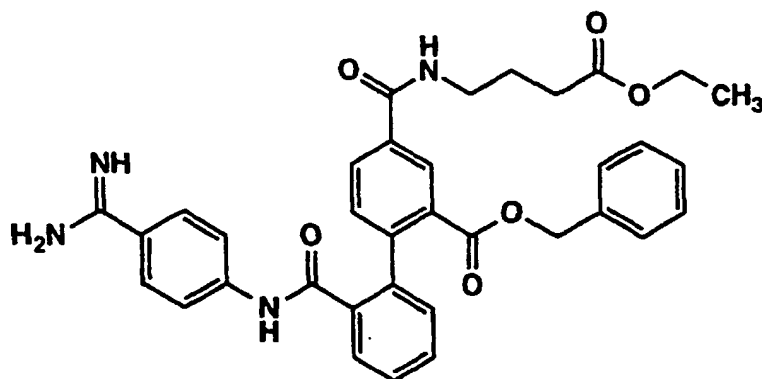
TLC : Rf 0.49 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (CD₃OD) : δ 8.30 (1H, d, J = 2.0 Hz), 7.95 (1H, dd, J = 8.0 Hz, 2.0 Hz), 7.68 (2H, d, J = 9.0 Hz), 7.66 (1H, dd, J = 7.5 Hz, 1.5 Hz), 7.59 (2H, d, J = 9.0 Hz), 7.58-7.46 (2H, m), 7.42 (1H, d, J = 8.0 Hz), 7.30-7.23 (4H, m), 7.18-7.10 (2H, m), 5.12 (2H, s), 3.66 (3H, s), 3.62 (2H, t, J = 7.0 Hz), 2.64 (2H, t, J = 7.0 Hz).

Example 7(96)

Benzyl 2'-(4-amidinophenylcarbamoyl)-4-((3-ethoxycarbonylpropyl)carbamoyl)-2-biphenylcarboxylate

[0210]



TLC : Rf 0.54 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (CD₃OD) : δ 8.32 (1H, d, J = 2.0 Hz), 7.96 (1H, dd, J = 8.0 Hz, 2.0 Hz), 7.68 (2H, d, J = 9.0 Hz), 7.66 (1H, dd, J = 7.5 Hz, 1.5 Hz), 7.58 (2H, d, J = 9.0 Hz), 7.58-7.46 (2H, m), 7.42 (1H, d, J = 8.0 Hz), 7.30-7.22 (4H, m), 7.18-7.12 (2H, m), 5.13 (2H, s), 4.07 (2H, q, J = 7.0 Hz), 3.40 (2H, t, J = 7.0 Hz), 2.38 (2H, t, J = 7.0 Hz), 1.90 (2H, quint, J = 7.0 Hz), 1.20 (3H, t, J = 7.0 Hz).

Example 7(97)

Benzyl 2'-(4-amidinophenylcarbamoyl)-4-((1-t-butoxycarbonylpyperidin-4-ylmethyl)carbamoyl)-2-biphenylcarboxylate

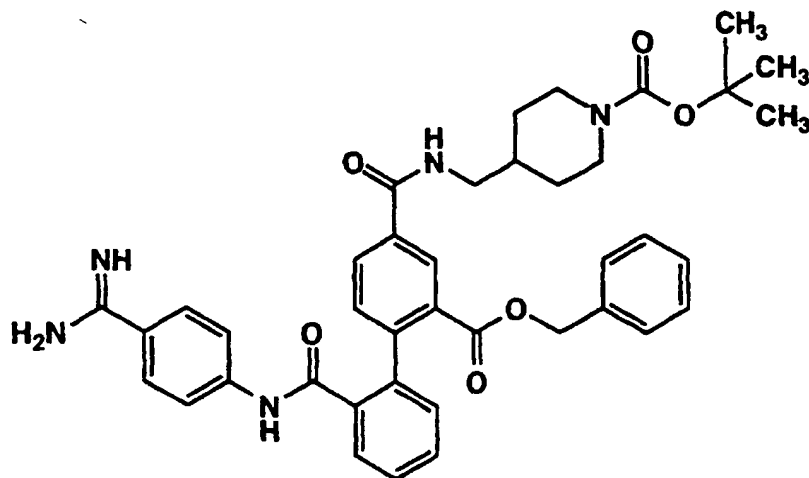
5 [0211]

10

15

20

25



30

TLC : Rf 0.52 (Chloroform : Methanol : Water = 8 : 2 : 0.1) ;

NMR (CD₃OD) : δ 8.31 (1H, d, J = 1.5 Hz), 7.97 (1H, dd, J = 1.5, 7.8 Hz), 7.69-7.59 (5H, m), 7.53-7.50 (2H, m), 7.43 (1H, d, J = 8.1 Hz), 7.28-7.26 (4H, m), 7.16-7.14 (2H, m), 5.13 (2H, s), 4.07 (2H, d, J = 12.9 Hz), 3.27-3.23 (2H, m), 2.74 (2H, m), 1.90-1.70 (3H, m), 1.45 (9H, s), 1.20-1.05 (2H, m).

Example 7(98)

35

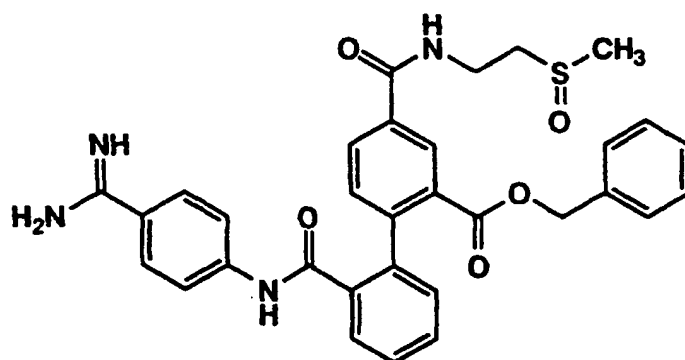
Benzyl 2'-(4-amidinophenylcarbamoyl)-4-((2-methylsulfinylethyl)carbamoyl)-2-biphenylcarboxylate

[0212]

40

45

50



55

TLC : Rf 0.64 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d₆-DMSO) : δ 10.63 (1H, s), 9.4-9.0 (3H, br), 9.03 (1H, br.t), 8.26 (1H, d, J = 2.0 Hz), 8.04 (1H, dd, J = 2.0,

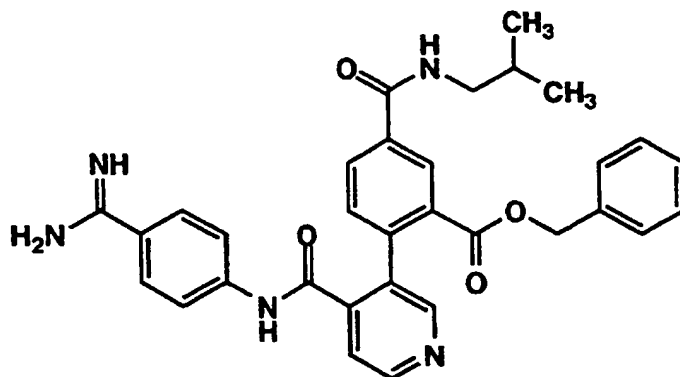
EP 1 078 917 A1

8.0 Hz), 7.8-7.6 (5H, m), 7.6-7.4 (2H, m), 7.42 (1H, d, J = 8.0 Hz), 7.4-7.2 (4H, m), 7.1-7.0 (2H, m), 5.04 (2H, s), 3.62 (2H, m), 3.06 (1H, dt, J = 13.0, 6.0 Hz), 2.87 (1H, dt, J = 13.0, 6.0 Hz), 2.58 (3H, s).

Example 7(99)

Benzyl 2-(4-(4-amidinophenylcarbamoyl)pyridin-3-yl)-5-((2-methylpropyl)carbamoyl)benzoate

[0213]



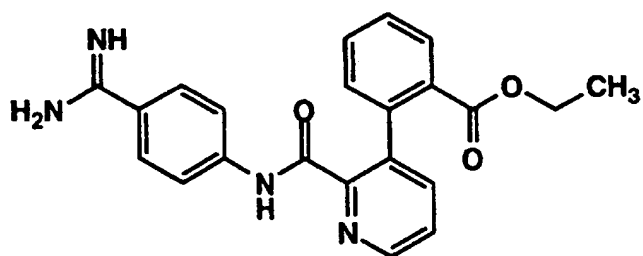
TLC : Rf 0.45 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (CD₃OD) : δ 8.63 (1H, d, J = 5.0 Hz), 8.50 (1H, s), 8.43 (1H, d, J = 2.0 Hz), 8.04 (1H, dd, J = 8.0 Hz, 2.0 Hz), 7.72 (2H, d, J = 9.0 Hz), 7.65 (2H, d, J = 9.0 Hz), 7.60 (1H, d, J = 5.0 Hz), 7.48 (1H, d, J = 8.0 Hz), 7.30-7.22 (3H, m), 7.22-7.13 (2H, m), 5.11 (2H, s), 3.19 (2H, d, J = 7.5 Hz), 2.02-1.81 (1H, m), 0.95 (6H, d, J = 6.5 Hz).

Example 7(100)

Ethyl 2-(2-(4-amidinophenylcarbamoyl)pyridin-3-yl)benzoate

[0214]



TLC : Rf 0.50 (Chloroform : Methanol : Water = 10 : 3 : 0.2) ;

NMR (d₆-DMSO) : δ 10.96 (1H, br.s), 9.18 (3H, br.s), 8.73 (1H, d, J = 4.4 Hz), 8.0-7.8 (1H, m), 7.92 (2H, d, J = 8.8 Hz), 7.80 (2H, d, J = 8.8 Hz), 7.8-7.6 (2H, m), 7.62 (1H, d, J = 7.2 Hz), 7.50 (1H, t, J = 7.2 Hz), 7.29 (1H, d, J = 7.2 Hz), 3.93 (2H, q, J = 7.4 Hz), 0.88 (3H, t, J = 7.4 Hz).

Example 7(101)

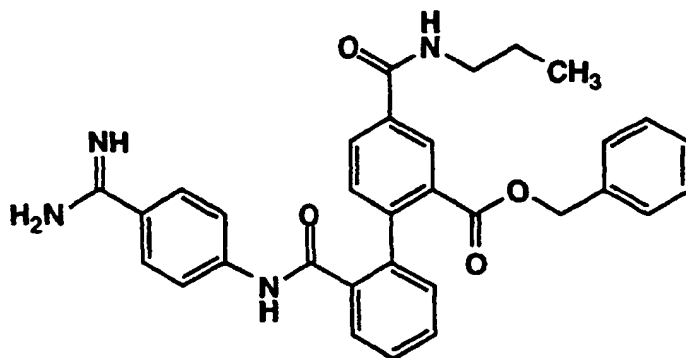
Benzyl 2'-(4-amidinophenylcarbamoyl)-4-propylcarbamoyl-2-biphenylcarboxylate

5 [0215]

10

15

20



25 TLC : Rf 0.38 (Chloroform : Methanol : Water = 8 : 2 : 0.1) ;
 NMR (CD₃OD) : δ 8.32 (1H, d, J = 1.8 Hz), 7.97 (1H, dd, J = 1.8, 8.0 Hz), 7.69-7.50 (8H, m), 7.42 (1H, d, J = 8.0 Hz), 7.29-7.26 (3H, m), 7.18-7.15 (2H, m), 5.13 (2H, s), 3.35-3.29 (2H, m), 1.62 (2H, sextet, J = 7.2 Hz), 0.96 (3H, t, J = 7.2 Hz).

Example 7(102)

30

Benzyl 2'-(4-amidinophenylcarbamoyl)-4-((3-hydroxy-2,2-dimethylpropyl)carbamoyl)-2-biphenylcarboxylate

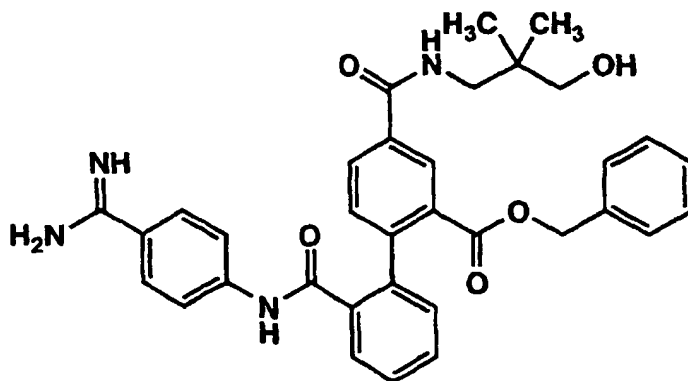
[0216]

35

40

45

50

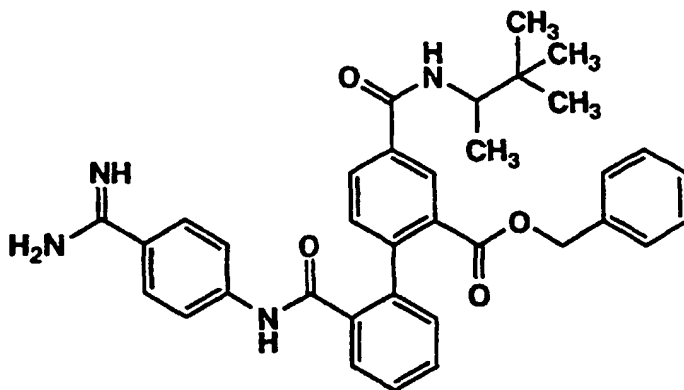


55 TLC : Rf 0.38 (Chloroform : Methanol : Water = 8 : 2 : 0.1) ;
 NMR (CD₃OD) : δ 8.33 (1H, d, J = 2.0 Hz), 7.98 (1H, dd, J = 2.0, 8.0 Hz), 7.70-7.58 (6H, m), 7.55-7.50 (2H, m), 7.43 (1H, d, J = 8.0 Hz), 7.29-7.26 (3H, m), 7.17-7.10 (2H, m), 5.13 (2H, s), 3.29-3.24 (4H, m), 0.92 (6H, s).

Example 7(103)

Benzyl 2'-(4-amidinophenylcarbamoyl)-4-((1,2,2-trimethylpropyl)carbamoyl)-2-biphenylcarboxylate

[0217]



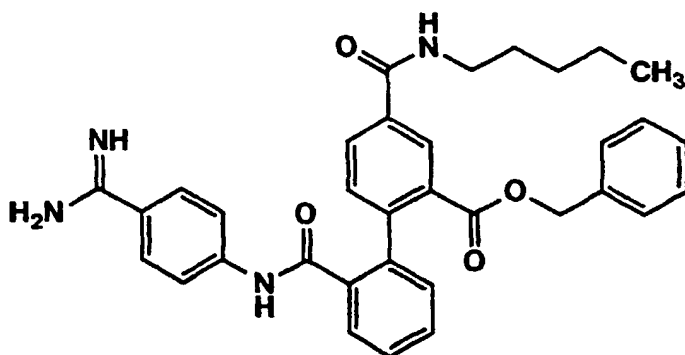
TLC : Rf 0.33 (Chloroform : Methanol : Water = 8 : 2 : 0.2) ;

NMR (CD₃OD) : δ 8.28 (1H, d, J = 1.8 Hz), 7.93 (1H, dd, J = 1.8, 8.0 Hz), 7.66-7.69 (3H, m), 7.61 (2H, d, J = 9.0 Hz), 7.50-7.54 (2H, m), 7.41 (1H, d, J = 8.0 Hz), 7.25-7.29 (4H, m), 7.14-7.17 (2H, m), 5.13 (2H, s), 4.05 (1H, q, J = 7.0 Hz), 1.16 (3H, d, J = 7.0 Hz), 0.96 (9H, s).

Example 7(104)

Benzyl 2'-(4-amidinophenylcarbamoyl)-4-pentylcarbamoyl-2-biphenylcarboxylate

[0218]



TLC : Rf 0.32 (Chloroform : Methanol : Water = 8 : 2 : 0.2) ;

NMR (CD₃OD) : δ 8.31 (1H, d, J = 2.0 Hz), 7.96 (1H, dd, J = 2.0, 8.0 Hz), 7.66-7.68 (3H, m), 7.61 (2H, d, J = 9.0 Hz), 7.50-7.54 (2H, m), 7.42 (1H, d, J = 8.0 Hz), 7.26-7.28 (4H, m), 7.14-7.17 (2H, m), 5.13 (2H, s), 3.35 (2H, t, J = 7.0 Hz), 1.59-1.63 (2H, m), 1.33-1.38 (4H, m), 0.90-0.95 (3H, m).

Example 7(105)

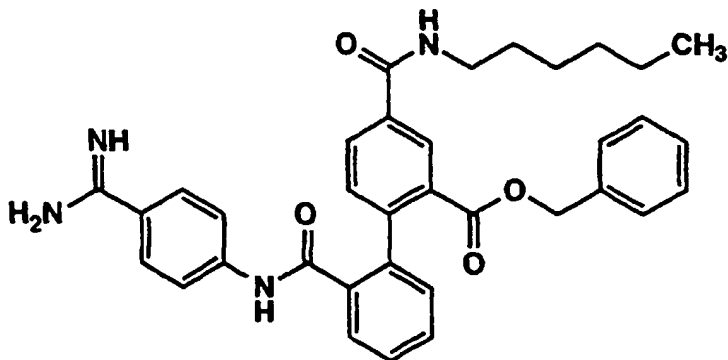
Benzyl 2'-(4-amidinophenylcarbamoyl)-4-hexylcarbamoyl-2-biphenylcarboxylate

5 [0219]

10

15

20



25

TLC : Rf 0.48 (Chloroform : Methanol : Water = 8 : 2 : 0.1) ;

NMR (CD₃OD) : δ 8.32 (1H, d, J = 1.8 Hz), 7.97 (1H, dd, J = 1.8, 8.0 Hz), 7.70-7.49 (8H, m), 7.42 (1H, d, J = 8.0 Hz), 7.29-7.26 (3H, m), 7.18-7.13 (2H, m), 5.13 (2H, s), 3.39-3.30 (2H, m), 1.70-1.50 (2H, m), 1.50-1.20 (6H, m), 0.90 (3H, t, J = 6.6 Hz).

Example 7(106)

30

Benzyl 2'-(4-amidinophenylcarbamoyl)-4-((1, 2-dimethylpropyl)carbamoyl)-2-biphenylcarboxylate

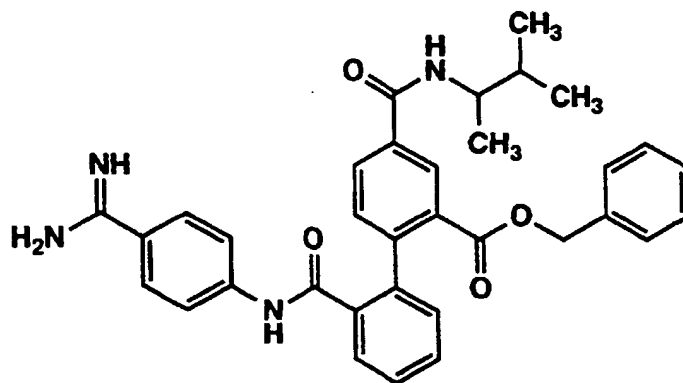
[0220]

35

40

45

50



55

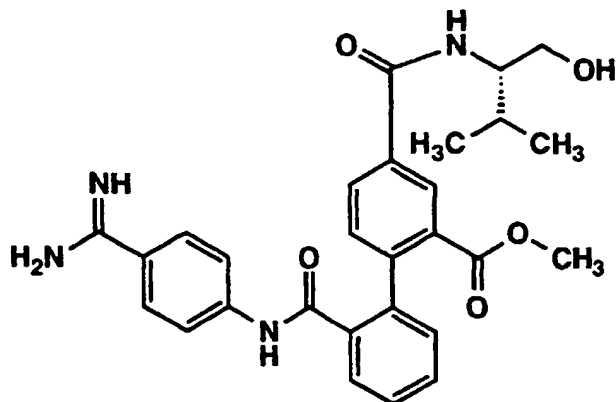
TLC : Rf 0.45 (Chloroform : Methanol : Water = 8 : 2 : 0.1) ;

NMR (CD₃OD) : δ 8.31 (1H, d, J = 1.8 Hz), 7.96 (1H, dd, J = 1.8, 8.0 Hz), 7.70-7.50 (8H, m), 7.41 (1H, d, J = 8.0 Hz), 7.29-7.26 (3H, m), 7.18-7.13 (2H, m), 5.14 (2H, s), 3.91 (1H, m), 1.80 (1H, sextet, J = 6.6 Hz), 1.18 (3H, d, J = 6.6 Hz), 0.95 (6H, d, J = 6.6 Hz).

Example 7(107)

Methyl 2'-(4-amidinophenylcarbamoyl)-4-(((1S)-1-hydroxymethyl-2-methylpropyl)carbamoyl)-2-biphenylcarboxylate

[0221]



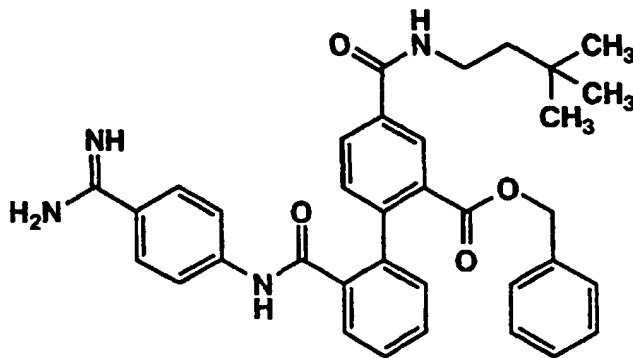
TLC : Rf 0.49 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d₆-DMSO) : δ 10.63 (1H, s), 9.3-8.8 (3H, br), 8.24 (1H, d, J = 1.8 Hz), 8.22 (1H, br.d, J = 9.3 Hz), 8.06 (1H, dd, J = 1.8, 7.8 Hz), 7.75 (4H, like s), 7.68 (1H, dd, J = 1.8, 7.8 Hz), 7.60 (1H, dt, J = 1.8, 7.8 Hz), 7.54 (1H, dt, J = 1.8, 7.8 Hz), 7.40 (1H, d, J = 7.8 Hz), 7.31 (1H, dd, J = 1.8, 7.8 Hz), 4.60 (1H, t, J = 6.0 Hz), 3.81 (1H, m), 3.54 (3H, s), 3.6-3.4 (2H, m), 1.90 (1H, like sextet, J = 6.9 Hz), 0.90 (3H, d, J = 6.9 Hz), 0.87 (3H, d, J = 6.9 Hz).

Example 7(108)

Benzyl 2'-(4-amidinophenylcarbamoyl)-4-((3, 3-dimethylbutyl)carbamoyl)-2-biphenylcarboxylate

[0222]



TLC : Rf 0.28 (Chloroform : Methanol : Water = 8 : 2 : 0.2) ;

NMR (CD₃OD) : δ 8.32 (1H, d, J = 2.0 Hz), 7.95 (1H, dd, J = 2.0, 8.0 Hz), 7.65-7.69 (3H, m), 7.60 (2H, d, J = 9.0 Hz), 7.49-7.53 (2H, m), 7.40 (1H, d, J = 8.0 Hz), 7.24-7.28 (4H, m), 7.13-7.16 (2H, m), 5.12 (2H, s), 3.35-3.41 (2H, m), 1.50-1.55 (2H, m), 0.97 (9H, s).

Example 7(109)

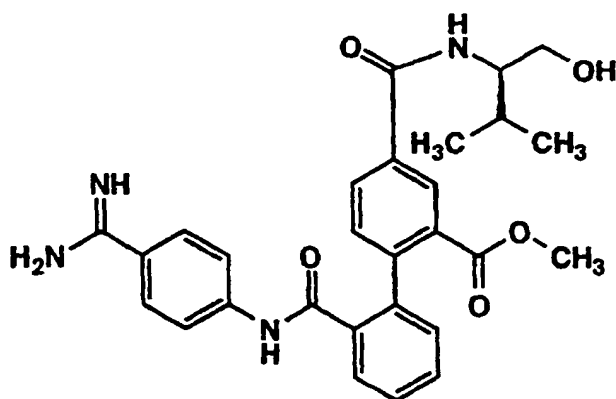
Methyl 2'-(4-amidinophenylcarbamoyl)-4-(((1R)-1-hydroxymethyl-2-methylpropyl)carbamoyl)-2-biphenylcarboxylate

5 [0223]

10

15

20



25

TLC : Rf 0.49 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d_6 -DMSO) : δ 10.63 (1H, br.s), 9.3-8.8 (3H, br), 8.24 (1H, d, J = 1.5 Hz), 8.22 (1H, d, J = 8.0 Hz), 8.06 (1H, dd, J = 1.5, 8.0 Hz), 7.75 (4H, like s), 7.68 (1H, dd, J = 1.5, 8.0 Hz), 7.60 (1H, dt, J = 1.5, 8.0 Hz), 7.54 (1H, dt, J = 1.5, 8.0 Hz), 7.40 (1H, d, J = 8.0 Hz), 7.32 (1H, dd, J = 1.5, 8.0 Hz), 4.61 (1H, t, J = 7.8 Hz), 3.81 (1H, m), 3.54 (3H, s), 3.6-3.4 (2H, m), 1.90 (1H, like sextet, J = 6.8 Hz), 0.90 (3H, d, J = 6.8 Hz), 0.86 (3H, d, J = 6.8 Hz);

30

Example 7(110)

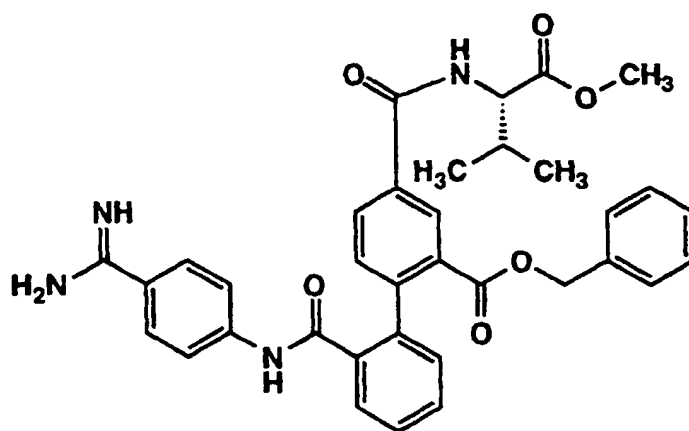
Benzyl 2'-(4-amidinophenylcarbamoyl)-4-(((1S)-1-methoxycarbonyl-2-methylpropyl)carbamoyl)-2-biphenylcarboxylate

35 [0224]

40

45

50



55

TLC : Rf 0.45 (Chloroform : Methanol : Water = 8 : 2 : 0.1) ;

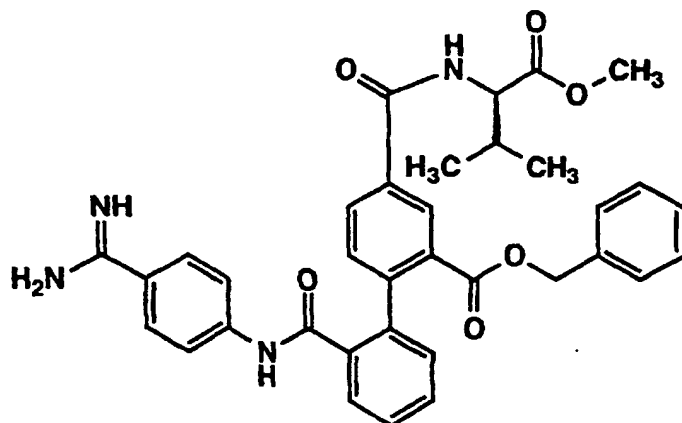
NMR (CD_3OD) : δ 8.32 (1H, d, J = 1.4 Hz), 8.00 (1H, dd, J = 1.4, 8.0 Hz), 7.70-7.58 (5H, m), 7.55-7.49 (2H, m),

7.43 (1H, d, J = 8.0 Hz), 7.30-7.25 (4H, m), 7.17-7.12 (2H, m), 5.12 (2H, s), 4.46 (1H, d, J = 7.0 Hz), 3.73 (3H, s), 2.24 (1H, sextet, J = 7.0 Hz), 1.01 (6H, dd, J = 3.6, 7.0 Hz).

Example 7(111)

Benzyl 2'-(4-amidinophenylcarbamoyl)-4-(((1R)-1-methoxycarbonyl-2-methylpropyl)carbamoyl)-2-biphenylcarboxylate

[0225]



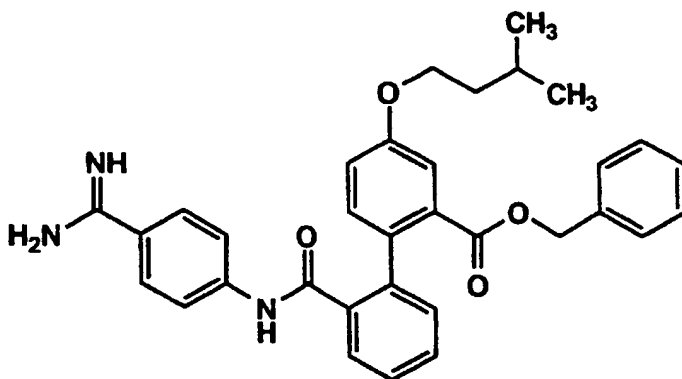
TLC : Rf 0.48 (Chloroform : Methanol : Water = 8 : 2 : 0.1) ;

NMR (CD₃OD) : δ 8.32 (1H, d, J = 2.1 Hz), 7.99 (1H, dd, J = 2.1, 8.1 Hz), 7.69-7.50 (7H, m), 7.43 (1H, d, J = 8.1 Hz), 7.29-7.25 (4H, m), 7.16-7.13 (2H, m), 5.12 (2H, s), 4.46 (1H, d, J = 6.9 Hz), 3.73 (3H, s), 2.24 (1H, sextet, J = 6.9 Hz), 1.01 (6H, dd, J = 5.1, 6.9 Hz).

Example 7(112)

Benzyl 2'-(4-amidinophenylcarbamoyl)-4-(3-methylbutoxy)-2-biphenylcarboxylate

[0226]



EP 1 078 917 A1

TLC : Rf 0.51 (Chloroform : Methanol : Water = 8 : 2 : 0.1) ;

NMR (CD₃OD) : δ 7.69-7.41 (7H, m), 7.34-7.04 (9H, m), 5.12 (2H, s), 4.01 (2H, t, J = 6.6 Hz), 1.88-1.59 (3H, m), 0.94 (6H, d, J = 6.6 Hz).

5 Example 7(113)

Benzyl 2-(3-(4-amidinophenylcarbamoyl)pyridin-4-yl)-5-((2-methylpropyl)carbamoyl)benzoate

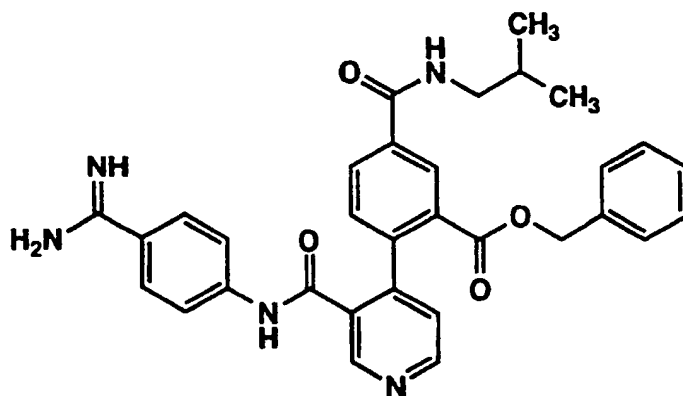
[0227]

10

15

20

25



30

TLC : Rf 0.33 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (CD₃OD) : δ 8.77 (1H, s), 8.63 (1H, dd, J = 5.0 Hz), 8.43 (1H, d, J = 2.0 Hz), 8.04 (1H, dd, J = 8.0 Hz, 2.0 Hz), 7.70 (4H, s), 7.43 (1H, d, J = 8.0 Hz), 7.38 (1H, d, J = 5.0 Hz), 7.30-7.12 (5H, m), 5.11 (2H, s), 3.19 (2H, d, J = 7.0 Hz), 2.02-1.81 (1H, m), 0.95 (6H, d, J = 6.5 Hz).

35

40

45

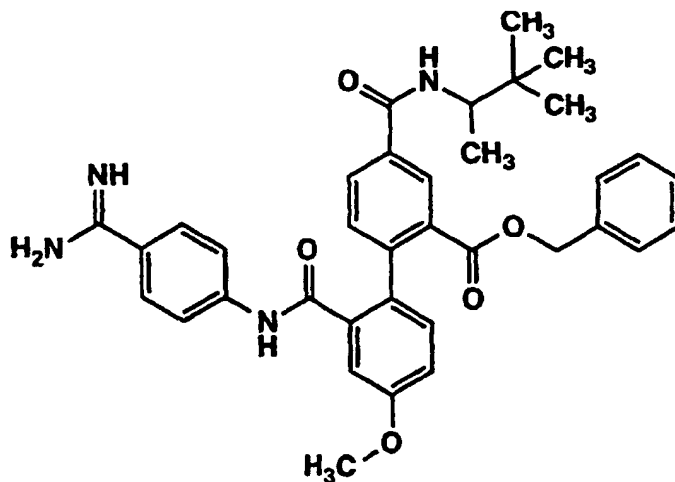
50

55

Example 7(114)

Benzyl 2'-(4-amidinophenylcarbamoyl)-4'-methoxy-4-((1, 2, 2-trimethylpropyl)carbamoyl)-2-biphenylcarboxylate

[0228]



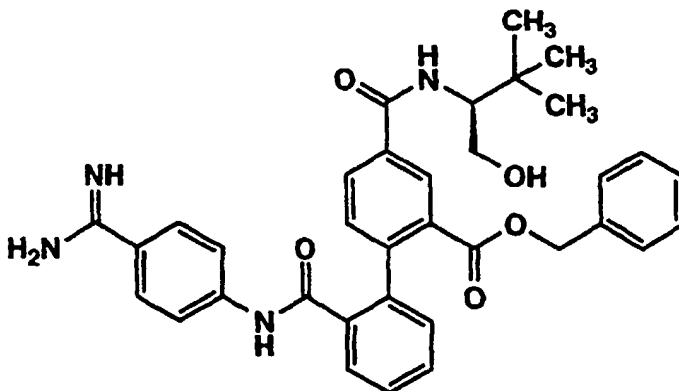
TLC : Rf 0.67 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (CD₃OD) : δ 8.77 (1H, d, J = 2.5 Hz), 8.25 (1H, d, J = 2.0 Hz), 8.18 (1H, dd, J = 8.5 Hz, 2.5 Hz), 8.02 (1H, d, J = 8.5 Hz), 7.93 (1H, dd, J = 8.0 Hz, 2.0 Hz), 7.42 (1H, d, J = 8.0 Hz), 7.27-7.17 (5H, m), 7.26-7.09 (2H, m), 7.08 (1H, dd, J = 8.5 Hz, 2.5 Hz), 5.10 (2H, s), 4.05 (1H, q, J = 7.0 Hz), 3.89 (3H, s), 1.15 (3H, d, J = 7.0 Hz), 0.95 (9H, s).

Example 7(115)

Benzyl 2'-(4-amidinophenylcarbamoyl)-4-(((1S)-1-hydroxymethyl-2, 2-dimethylpropyl)carbamoyl)-2-biphenylcarboxylate

[0229]



TLC : Rf 0.32 (Chloroform : Methanol : Water = 8 : 2 : 0.1) ;

NMR (CD₃OD) : δ 8.33 (1H, d, J = 1.8 Hz), 7.99 (1H, dd, J = 1.8, 7.8 Hz), 7.70-7.49 (7H, m), 7.42 (1H, d, J = 8.0 Hz), 7.29-7.25 (4H, m), 7.18-7.13 (2H, m), 5.13 (2H, s), 4.04 (1H, dd, J = 3.6, 9.2 Hz), 3.87 (1H, dd, J = 3.6, 11.8 Hz), 3.61 (1H, dd, J = 9.0, 11.8 Hz), 0.98 (9H, s).

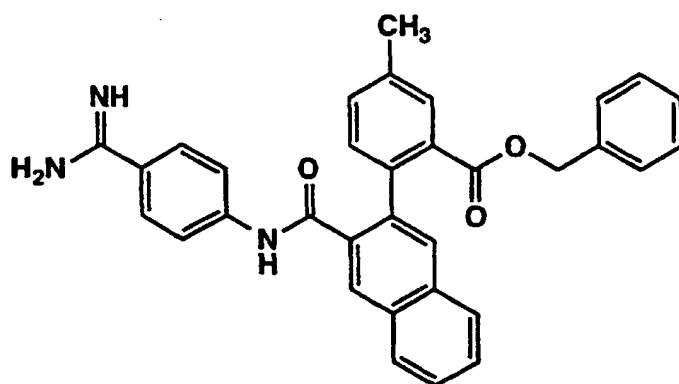
Example 8 - Example 8(7)

[0230] The following compounds were obtained by the same procedure as a series of reaction of Reference Example 7 \rightarrow Reference Example 8 \rightarrow Example 1, using a compound prepared in Reference Example 5 or a corresponding compound, with the proviso that, the compound of Example 8(6) was obtained by the same procedure as a series of reaction of Reference Example 3 instead of Example 1.

Example 8

Benzy 2-(3-(4-amidinophenylcarbamoyl)naphthalen-2-yl)-5-methylbenzoate

[0231]



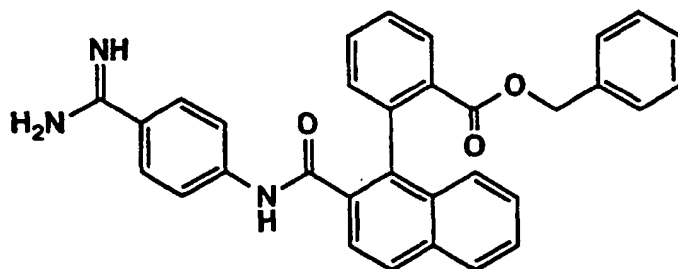
TLC : Rf 0.20 (Chloroform : Methanol = 4 : 1) ;

NMR (CD₃OD) : δ 8.16 (1H, s), 8.1-8.0 (1H, m), 7.9-7.8 (1H, m), 7.7-7.6 (8H, m), 7.39 (1H, dd, J = 6.6, 1.8 Hz), 7.29 (1H, d, J = 7.6 Hz), 7.2-7.0 (3H, m), 6.94 (2H, dd, J = 7.6, 1.0 Hz), 5.06 (2H, s), 2.39 (3H, s).

Example 8(1)

Benzy 2-(2-(4-amidinophenylcarbamoyl)naphthalen-1-yl)benzoate

[0232]



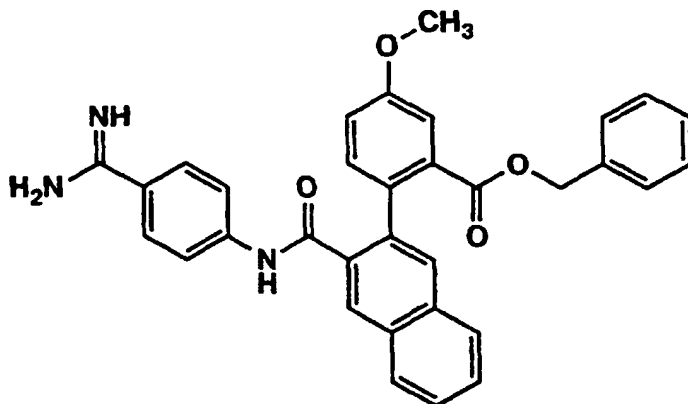
TLC : Rf 0.75 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (CD₃OD) : δ 8.03-7.92 (3H, m), 7.69-7.46 (8H, m), 7.42-7.10 (6H, m), 6.93-6.89 (2H, m), 5.02 (1H, d, J = 12 Hz), 4.95 (1H, d, J = 12 Hz).

Example 8(2)

Benzyl 2-(3-(4-amidinophenylcarbamoyl)naphthalen-2-yl)-5-methoxybenzoate

[0233]



TLC : Rf 0.58 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (CD₃OD) : δ 8.14 (1H, s), 8.02-7.97 (1H, m), 7.88-7.83 (1H, m), 7.73-7.58 (7H, m), 7.41 (1H, d, J = 2.5 Hz), 7.33 (1H, d, J = 8.0 Hz), 7.16-6.87 (6H, m), 5.05 (2H, s), 3.82 (3H, s).

Example 8(3)

Benzyl 2-(3-(4-amidinophenylcarbamoyl)naphthalen-2-yl)-5-propoxybenzoate

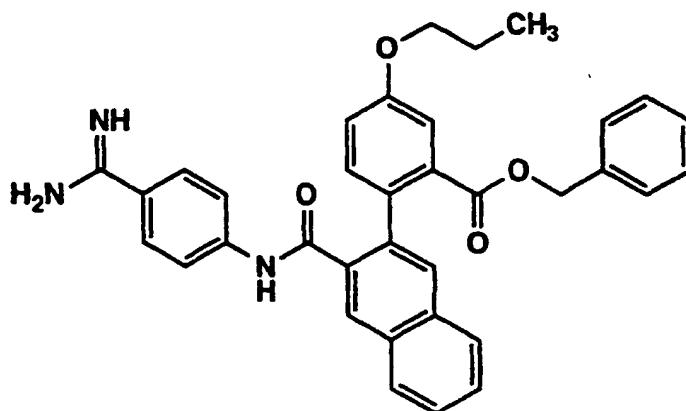
5 [0234]

10

15

20

25



30

TLC : Rf 0.58 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (CD₃OD) : δ 8.14 (1H, s), 8.03-7.97 (1H, m), 7.89-7.83 (1H, m), 7.73-7.58 (7H, m), 7.39 (1H, d, J = 2.5 Hz), 7.32 (1H, d, J = 8.0 Hz), 7.16-6.87 (6H, m), 5.05 (2H, s), 3.96 (2H, t, J = 7.9 Hz), 1.79 (2H, sextet, J = 7.0 Hz), 1.03 (3H, t, J = 7.0 Hz).

Example 8(4)

Benzyl 2'-(4-amidinophenylcarbamoyl)-4'-chloro-2-biphenylcarboxylate

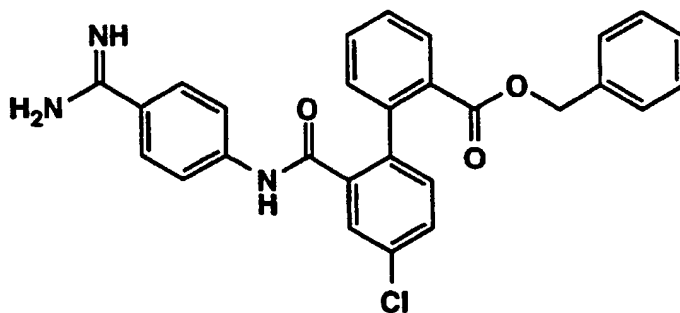
35

[0235]

40

45

50



55

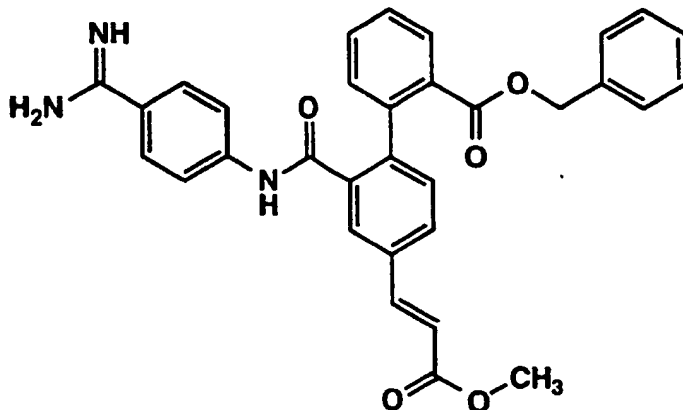
TLC : Rf 0.24 (Chloroform : Methanol : Water = 8 : 2 : 0.2) ;

NMR (CD₃OD) : δ 7.90 (1H, dd, J = 1.6, 7.8 Hz), 7.67 (2H, d, J = 9.2 Hz), 7.55-7.61 (3H, m), 7.39-7.52 (3H, m), 7.28-7.33 (4H, m), 7.20 (1H, d, J = 7.8 Hz), 7.14-7.17 (2H, m), 5.13 (2H, s).

Example 8(5)

Benzyl 2'-(4-amidinophenylcarbamoyl)-4'-((E)-2-methoxycarbonyl-ethenyl)-2-biphenylcarboxylate

[0236]



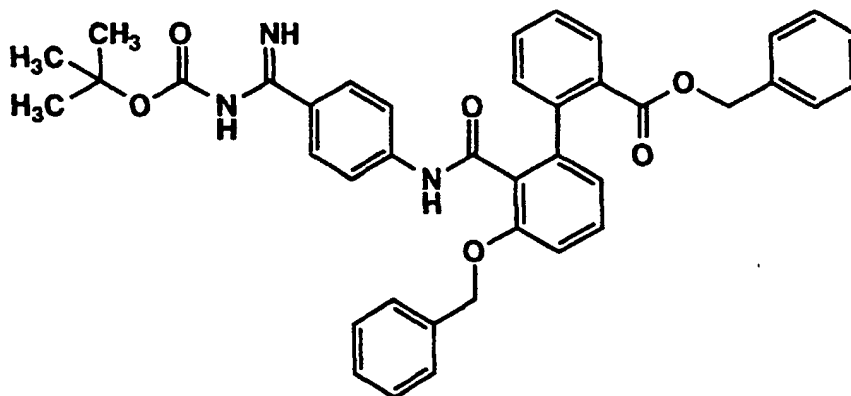
TLC : Rf 0.19 (Chloroform : Methanol = 4 : 1) ;

NMR (CDCl₃) : δ 9.25 (1H, s), 8.82 (2H, br s), 8.56 (2H, br s), 7.81 (1H, s), 7.9-7.7 (1H, m), 7.69 (2H, d, J = 7.8 Hz), 7.5-7.1 (13H, m), 7.07 (1H, d, J = 8.0 Hz), 6.48 (1H, d, J = 16.2 Hz), 5.11 (2H, s), 3.75 (3H, s).

Example 8(6)

Benzyl 2'-(4-(N¹-t-butoxycarbonylamidino)phenylcarbamoyl)-3'-benzyloxy-2-biphenylcarboxylate

[0237]



TLC : Rf 0.53 (Hexane : Ethyl acetate = 1 : 1) ;

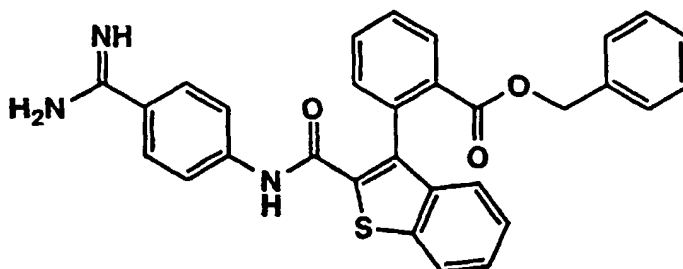
NMR (CDCl₃) : δ 9.80-9.00 (1H, broad), 8.37 (1H, s), 7.77 (1H, d, J = 8.0 Hz), 7.62 (2H, d, J = 9.0 Hz), 7.47-7.15 (15H, m), 7.09 (2H, d, J = 9.0 Hz), 7.02 (1H, d, J = 8.0 Hz), 6.72 (1H, d, J = 8.0 Hz), 5.21 (1H, d, J = 12 Hz), 5.20

(2H, s), 5.10 (1H, d, J = 12 Hz), 1.53 (9H, s).

Example 8(7)

5 Benzyl 2-(2-(4-amidinophenylcarbamoyl)benzothiophen-3-yl)benzoate

[0238]



TLC : Rf 0.72 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

25 NMR (CD₃OD) : δ 8.09 (1H, dd, J = 8.0, 1.5 Hz), 7.93 (1H, d, J = 8.0 Hz) 7.77-7.58 (4H, m), 7.56-7.41 (4H, m), 7.34 (1H, td, J = 7.0 Hz, 1.5 Hz), 7.26-7.08 (3H, m), 6.97-6.90 (2H, m), 5.02 (1H, d, J = 12 Hz), 4.95 (1H, d, J = 12 Hz).

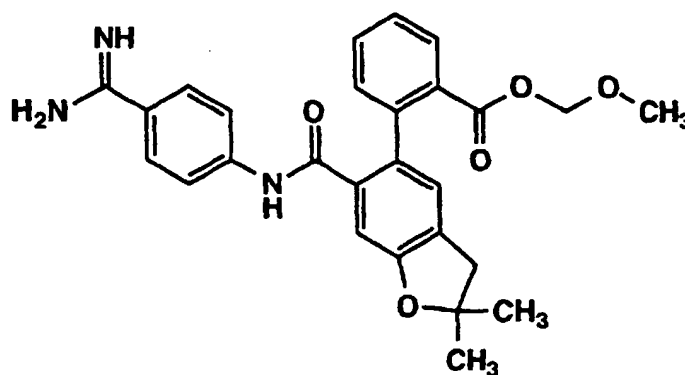
Example 9 — Example 9(31)

30 [0239] The following compounds were obtained by the same procedure as a series of reaction of Reference Example 6 → Example 2 → Example 1, using a compound prepared in Reference Example 5 or a corresponding compound.

Example 9

35 Methoxymethyl 2-(2, 3-dihydro-2, 2-dimethyl-6-(4-amidinophenylcarbamoyl) benzofuran-5-yl)benzoate

[0240]



55 TLC : Rf 0.33 (Chloroform : Methanol : Acetic acid = 20 : 2 : 1) ;

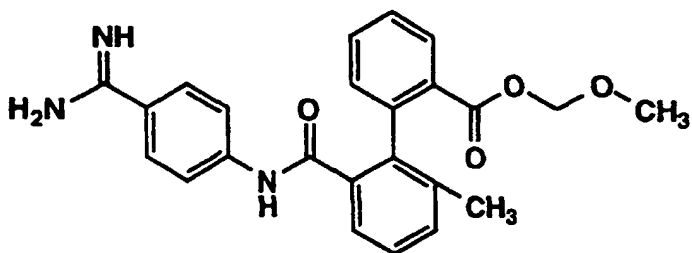
NMR (CD₃OD) : δ 7.83 (1H, d, J = 8 Hz), 7.69 (2H, d, J = 9 Hz), 7.58 (2H, d, J = 9 Hz), 7.51 (1H, t, J = 8 Hz), 7.38

(1H, t, J = 8 Hz), 7.31 (1H, d, J = 8 Hz), 7.05 (1H, s), 6.95 (1H, s), 5.28 (2H, s), 3.30 (3H, s), 3.10 (2H, s), 1.50 (6H, s).

Example 9(1)

Methoxymethyl 2'-(4-amidinophenylcarbamoyl)-6'-methyl-2-biphenylcarboxylate

[0241]

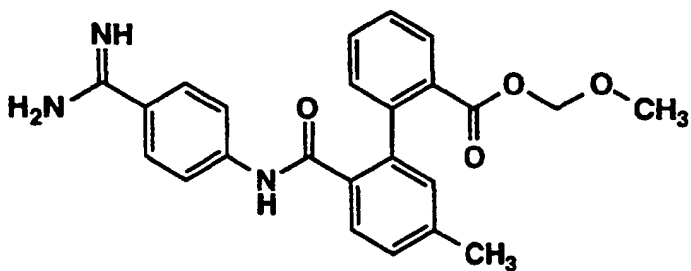


TLC : Rf 0.47 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) .

Example 9(2)

Methoxymethyl 2'-(4-amidinophenylcarbamoyl)-5'-methyl-2-biphenylcarboxylate

[0242]

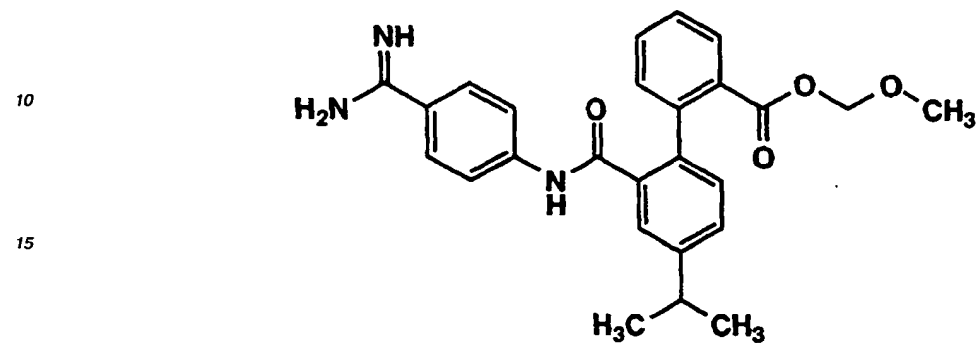


TLC : Rf 0.47 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) .

Example 9(3)

Methoxymethyl 2'-(4-amidinophenylcarbamoyl)-4'-isopropyl-2-biphenylcarboxylate

5 [0243]



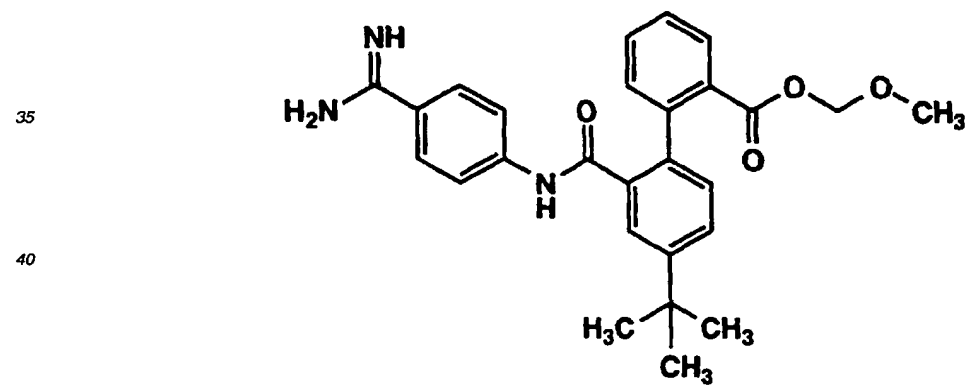
20

TLC : R_f 0.43 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) .

25 Example 9(4)

Methoxymethyl 2'-(4-amidinophenylcarbamoyl)-4'-t-butyl-2-biphenylcarboxylate

30 [0244]



40

45

TLC : R_f 0.41 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) .

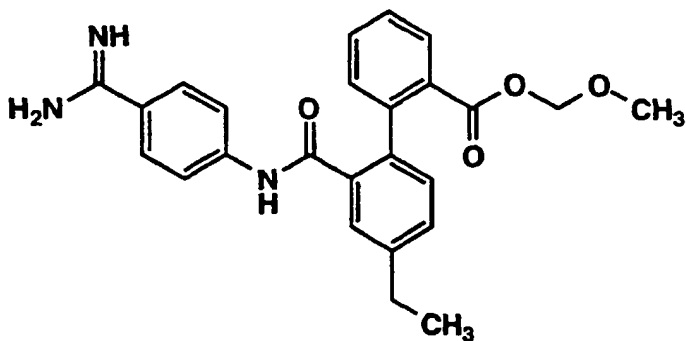
50

55

Example 9(5)

Methoxymethyl 2'-(4-amidinophenylcarbamoyl)-4'-ethyl-2-biphenylcarboxylate

[0245]

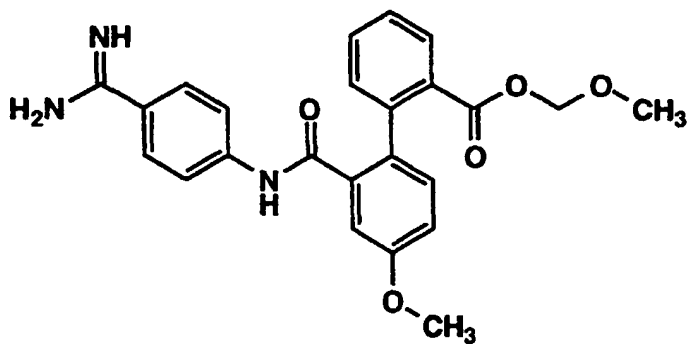


TLC : Rf 0.13 (Chloroform : Methanol : Water = 9 : 1 : 0.1) .

Example 9(6)

Methoxymethyl 2'-(4-amidinophenylcarbamoyl)-4'-methoxy-2-biphenylcarboxylate

[0246]



TLC : Rf 0.43 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) .

Example 9(7)

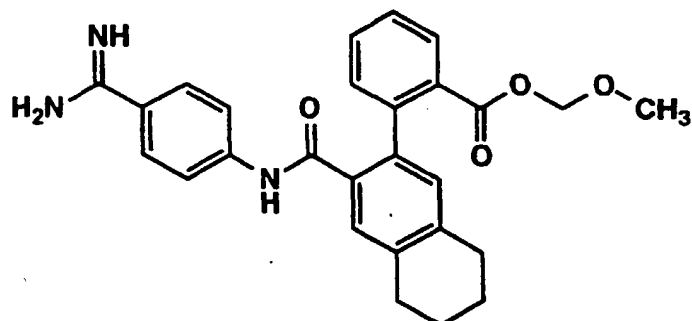
Methoxymethyl 2-(5, 6, 7, 8-tetrahydro-3-(4-amidinophenylcarbamoyl) naphthalen-2-yl)benzoate

5 [0247]

10

15

20



TLC : Rf 0.25 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) .

25 Example 9(8)

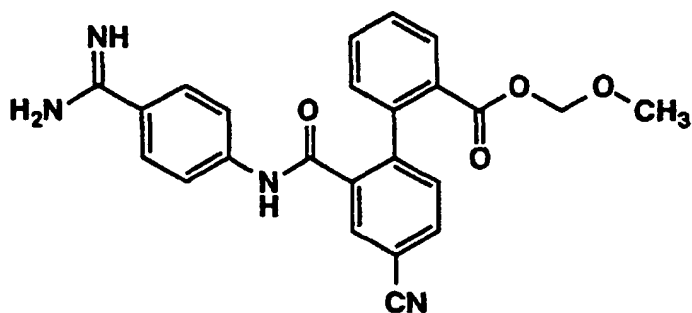
Methoxymethyl 2'-(4-amidinophenylcarbamoyl)-4'-cyano-2-biphenylcarboxylate

30 [0248]

30

35

40



45

TLC : Rf 0.12 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) .

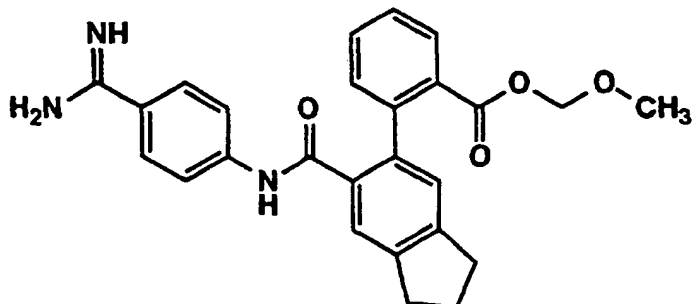
50

55

Example 9(9)

Methoxymethyl 2-(6-(4-amidinophenylcarbamoyl)indan-5-yl)benzoate

[0249]

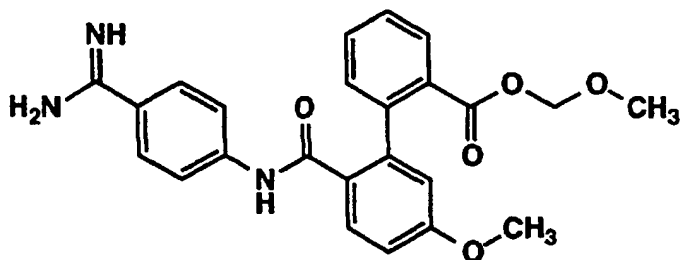


TLC : Rf 0.24 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) .

Example 9(10)

Methoxymethyl 2'-(4-amidinophenylcarbamoyl)-5'-methoxy-2-biphenylcarboxylate

[0250]



TLC : Rf 0.25 (Chloroform : Methanol : Water = 8 : 2 : 0.2) ;

NMR (CD₃OD) : δ 7.89 (1H, dd, J = 1.4, 8.0 Hz), 7.69 (2H, d, J = 9.0 Hz), 7.67 (1H, d, J = 8.6 Hz), 7.60 (2H, d, J = 9.0 Hz), 7.57 (1H, dt, J = 1.4, 8.0 Hz), 7.44 (1H, dt, J = 1.4, 8.0 Hz), 7.34 (1H, dd, J = 1.4, 8.0 Hz), 7.05 (1H, dd, J = 2.6, 8.6 Hz), 6.80 (1H, d, J = 2.6 Hz), 5.27 (2H, br.s), 3.87 (3H, s), 3.29 (3H, s).

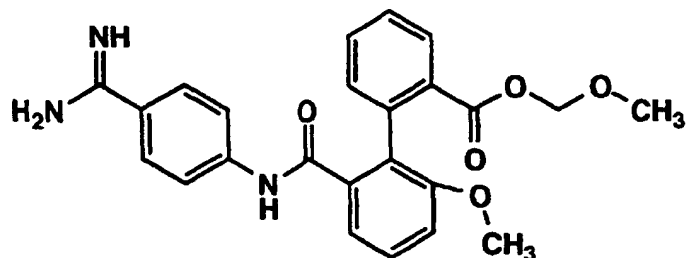
Example 9(11)

Methoxymethyl 2'-(4-amidinophenylcarbamoyl)-6'-methoxy-2-biphenylcarboxylate

5 [0251]

10

15



20

TLC : Rf 0.27 (Chloroform : Methanol : Water = 8 : 2 : 0.2) ;

NMR (CD₃OD) : δ 7.91 (1H, dd, J = 1.4, 7.6 Hz), 7.68 (2H, d, J = 9.2 Hz), 7.59 (2H, d, J = 9.2 Hz), 7.51 (1H, dt, J = 1.4, 7.6 Hz), 7.47 (1H, d, J = 7.6 Hz), 7.38 (1H, dt, J = 1.4, 7.6 Hz), 7.16-7.28 (3H, m), 5.32 (2H, s), 3.72 (3H, s), 3.35 (3H, s).

25

Example 9(12)

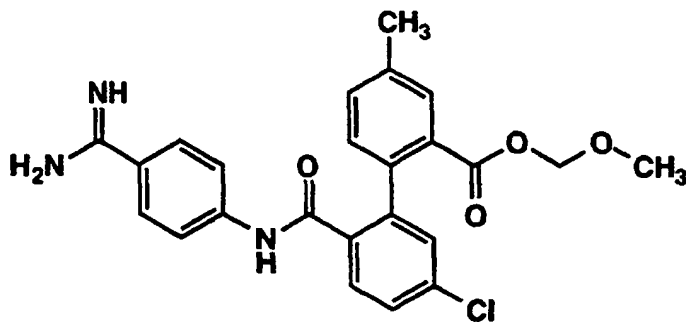
Methoxymethyl 2'-(4-amidinophenylcarbamoyl)-5'-chloro-4-methyl-2-biphenylcarboxylate

30

[0252]

35

40



45

TLC : Rf 0.27 (Chloroform : Methanol = 4 : 1) ;

NMR (CDCl₃) : δ 9.46 (1H, s), 8.70 (2H, s), 8.58 (2H, s), 7.72 (2H, d, J = 8.4 Hz), 7.62 (2H, d, J = 8.8 Hz), 7.44 (2H, d, J = 8.4 Hz), 7.4-7.2 (2H, m), 7.12 (1H, s), 7.09 (1H, d, J = 8.6 Hz), 5.27 (2H, d, J = 3.6 Hz), 3.32 (3H, s), 2.30 (3H, s).

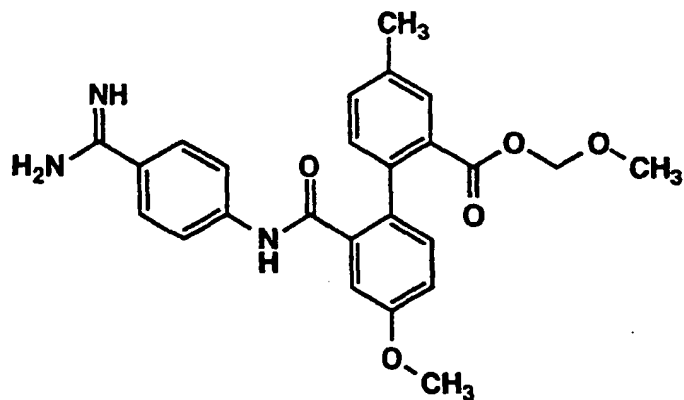
50

55

Example 9(13)

Methoxymethyl 2'-(4-amidinophenylcarbamoyl)-4'-methoxy-4-methyl-2-biphenylcarboxylate

[0253]



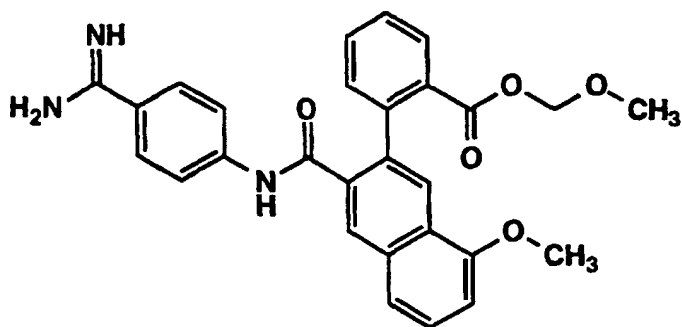
TLC : Rf 0.34 (Chloroform : Methanol = 4 : 1) ;

NMR (CDCl₃) : δ 9.34 (1H, s), 8.76 (2H, brs), 8.55 (2H, brs), 7.75 (2H, d, J = 8.4 Hz), 7.59 (1H, d, J = 1.4 Hz), 7.43 (2H, d, J = 8.4 Hz), 7.21 (1H, d, J = 8.4 Hz), 7.20 (1H, dd, J = 7.8, 1.4 Hz), 7.09 (1H, d, J = 7.8 Hz), 7.02 (1H, d, J = 8.4 Hz), 6.93 (1H, dd, J = 8.4, 2.4 Hz), 5.29 (2H, d, J = 6.2 Hz), 3.81 (3H, s), 3.33 (3H, s), 2.36 (3H, s).

Example 9(14)

Methoxymethyl 2-(3-(4-amidinophenylcarbamoyl)-8-methoxynaphthalen-2-yl)benzoate

[0254]



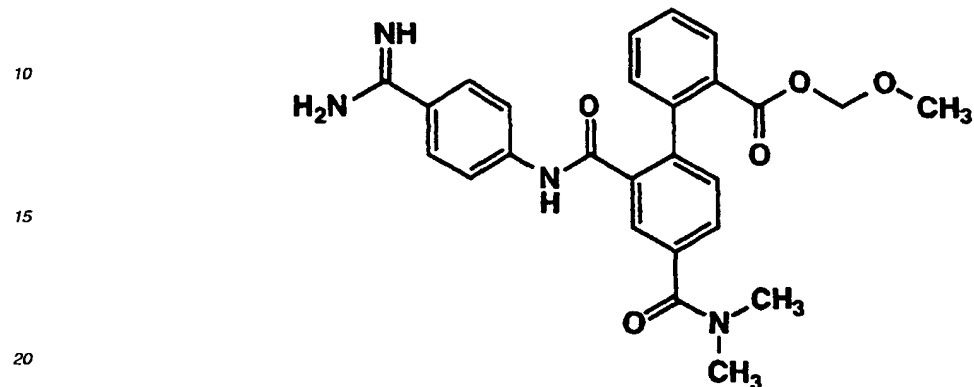
TLC : Rf 0.52 (Chloroform : Methanol : Water = 10 : 3 : 0.2) ;

NMR (d₆-DMSO) : δ 10.79 (1H, s), 9.4-8.9 (3H, br), 8.24 (1H, s), 7.97 (1H, s), 7.88 (1H, dd, J = 1.0, 7.6 Hz), 7.79 (4H, like s), 7.7-7.3 (5H, m), 7.10 (1H, d, J = 7.0 Hz), 5.08 (2H, br.s), 3.97 (3H, s), 3.05 (3H, s).

Example 9(15)

Methoxymethyl 2'-(4-amidinophenylcarbamoyl)-4'-dimethylcarbamoyl-2-biphenylcarboxylate

5 [0255]



25

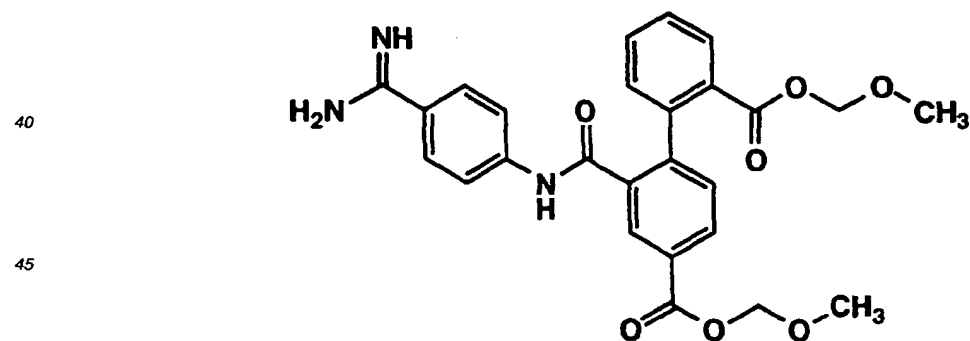
TLC : Rf 0.30 (Chloroform : Methanol : Water = 8 : 2 : 0.2) ;

NMR (CD₃OD) : δ 7.96 (1H, dd, J = 1.6, 7.8 Hz), 7.56-7.74 (7H, m), 7.35-7.51 (3H, m), 5.25 (2H, s), 3.30 (3H, s), 3.16 (3H, br.s), 3.13 (3H, br.s).

30 Example 9(16)

Bis(methoxymethyl) 2'-(4-amidinophenylcarbamoyl)-2, 4'-biphenyldicarboxylate

35 [0256]



50

TLC : Rf 0.27 (Chloroform : Methanol : Water = 8 : 2 : 0.2) ;

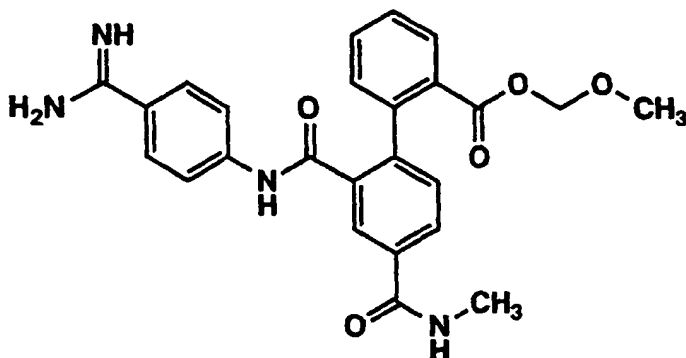
55

NMR (CD₃OD) : δ 8.33 (1H, d, J = 1.8 Hz), 8.24 (1H, dd, J = 1.8, 7.8 Hz), 7.98 (1H, dd, J = 1.4, 7.8 Hz), 7.73 (2H, d, J = 9.0 Hz), 7.67 (2H, d, J = 9.0 Hz), 7.62 (1H, dt, J = 1.4, 7.8 Hz), 7.48 (1H, dt, J = 1.4, 7.8 Hz), 7.47 (1H, d, J = 7.8 Hz), 7.37 (1H, dd, J = 1.4, 7.8 Hz), 5.53 (2H, s), 5.24 (2H, s), 3.57 (3H, s), 3.29 (3H, s).

Example 9(17)

Methoxymethyl 2'-(4-amidinophenylcarbamoyl)-4'-methylcarbamoyl-2-biphenylcarboxylate

[0257]



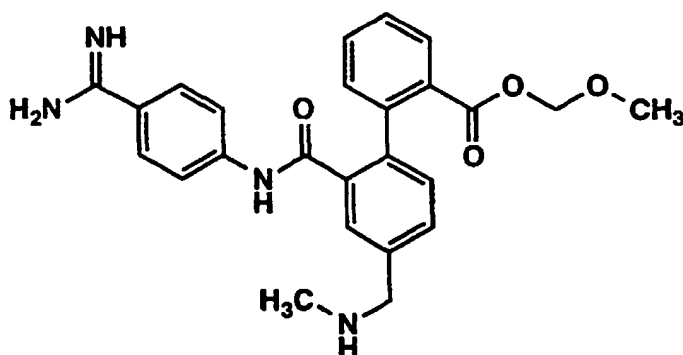
TLC : Rf 0.20 (Chloroform : Methanol : Water = 8 : 2 : 0.2) ;

NMR (CD₃OD) : δ 8.15 (1H, d, J = 1.8 Hz), 8.00 (1H, dd, J = 1.4, 8.0 Hz), 7.96 (1H, dd, J = 1.4, 8.0 Hz), 7.73 (2H, d, J = 9.0 Hz), 7.67 (2H, d, J = 9.0 Hz), 7.60 (1H, dt, J = 1.4, 8.0 Hz), 7.47 (1H, dt, J = 1.4, 8.0 Hz), 7.42 (1H, d, J = 8.0 Hz), 7.36 (1H, dd, J = 1.4, 8.0 Hz), 5.23 (2H, s), 3.26 (3H, s), 2.98 (3H, s).

Example 9(18)

Methoxymethyl 2'-(4-amidinophenylcarbamoyl)-4'-methylaminomethyl-2-biphenylcarboxylate

[0258]



TLC : Rf 0.26 (Chloroform : Methanol : Water = 8 : 2 : 0.2) ;

NMR (CD₃OD) : δ 7.90 (1H, dd, J = 1.8, 7.8 Hz), 7.53-7.73 (6H, m), 7.39-7.48 (2H, m), 7.33 (1H, dd, J = 1.8, 7.8 Hz), 7.29 (1H, d, J = 7.8 Hz), 5.26 (2H, s), 4.56 (2H, s), 3.29 (3H, s), 2.92 (3H, s), 1.50 (9H, s).

Example 9(19)

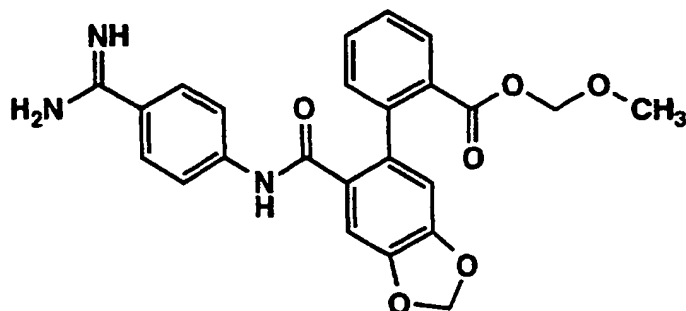
Methoxymethyl 2-(6-(4-amidinophenylcarbamoyl)-1, 2-methylenedioxy benzen-5-yl)benzoate

5 [0259]

10

15

20



25 TLC : Rf 0.53 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;
 NMR (CD₃OD) : δ 7.86 (1H, dd, J = 8.0 Hz, 1.5 Hz), 7.68 (2H, d, J = 9.0 Hz), 7.56 (2H, d, J = 9.0 Hz), 7.54 (1H, td, J = 8.0 Hz, 1.5 Hz), 7.40 (1H, td, J = 8.0 Hz, 1.5 Hz), 7.32 (1H, dd, J = 8.0 Hz, 1.5 Hz), 7.15 (1H, s), 6.74 (1H, s), 6.09 (2H, s), 5.29 (2H, s), 3.36 (3H, s).

Example 9(20)

30

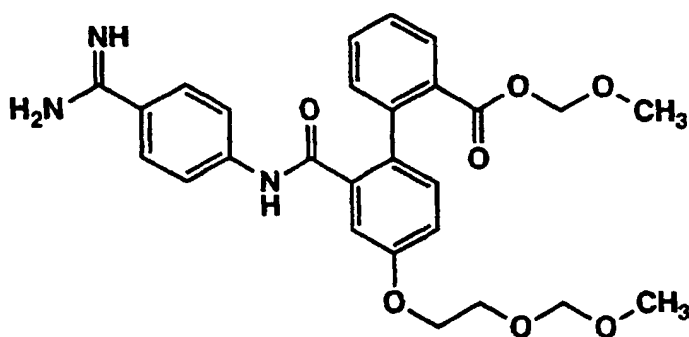
Methoxymethyl 2'-(4-amidinophenylcarbamoyl)-4'-(2-methoxymethoxyethoxy)-2-biphenylcarboxylate

[0260]

35

40

45



50

55

TLC : Rf 0.66 (Chloroform : Methanol : Water = 10 : 2 : 0.1) ;
 NMR (d₆-DMSO) : δ 10.51 (1H, s), 9.3-8.9 (3H, br.d), 7.9-7.6 (5H, m), 7.56 (1H, dt, J = 1.6, 7.4 Hz), 7.42 (1H, dt, J = 1.6, 7.4 Hz), 7.4-7.1 (4H, m), 5.11 (2H, br.s), 4.65 (2H, s), 4.24 (2H, t, J = 5.0 Hz), 3.83 (2H, t, J = 5.0 Hz), 3.29 (3H, s), 3.16 (3H, s).

Example 9(21)

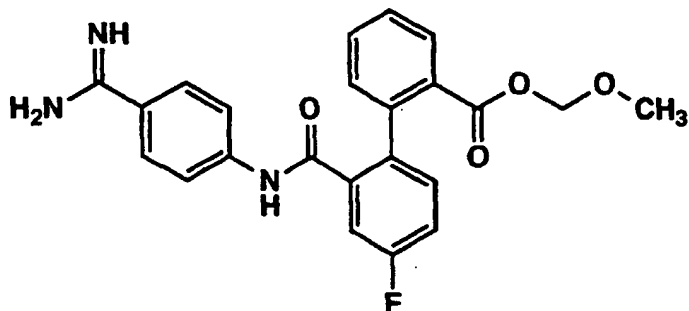
Methoxymethyl 2'-(4-amidinophenylcarbamoyl)-4'-fluoro-2-biphenylcarboxylate

5 [0261]

10

15

20



25 TLC : Rf 0.29 (Chloroform : Methanol : Water = 8 : 2 : 0.2) ;
 NMR (CD₃OD) : δ 7.92 (1H, dd, J = 1.6, 7.8 Hz), 7.71 (2H, d, J = 9.2 Hz), 7.63 (2H, d, J = 9.2 Hz), 7.56 (1H, m),
 7.40-7.49 (2H, m), 7.30-7.37 (3H, m), 5.26 (2H, s), 3.31 (3H, s).

Example 9(22)

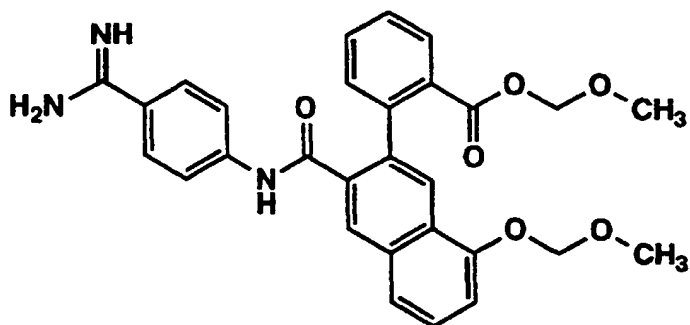
30 Methoxymethyl 2-(3-(4-amidinophenylcarbamoyl)-8-methoxymethoxy naphthalen-2-yl)benzoate

[0262]

35

40

45



50

TLC : Rf 0.49 (Chloroform : Methanol : Water = 10 : 3 : 0.2) .

55

Example 9(23)

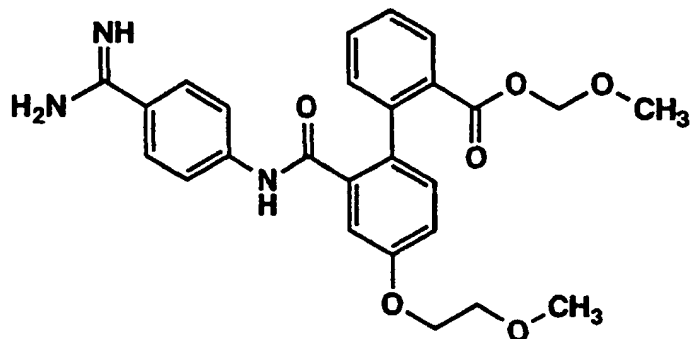
Methoxymethyl 2'-(4-amidinophenylcarbamoyl)-4'-(2-methoxyethoxy)-2-biphenylcarboxylate

5 [0263]

10

15

20



25 TLC : Rf 0.70 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;
 NMR (d_6 -DMSO) : δ 10.50 (1H, s), 9.3-8.9 (3H, br), 7.81 (1H, dd, J = 1.4, 7.8 Hz), 7.74 (4H, like s), 7.56 (1H, dt, J = 1.4, 7.4 Hz), 7.42 (1H, dt, J = 1.4, 7.4 Hz), 7.35-7.10 (4H, m), 5.11 (2H, br.s), 4.21 (2H, t, J = 4.4 Hz), 3.69 (2H, t, J = 4.4 Hz), 3.32 (3H, s), 3.16 (3H, s).

Example 9(24)

30

Methoxymethyl 2'-(4-amidinophenylcarbamoyl)-4'-trifluoromethoxy-2-biphenylcarboxylate

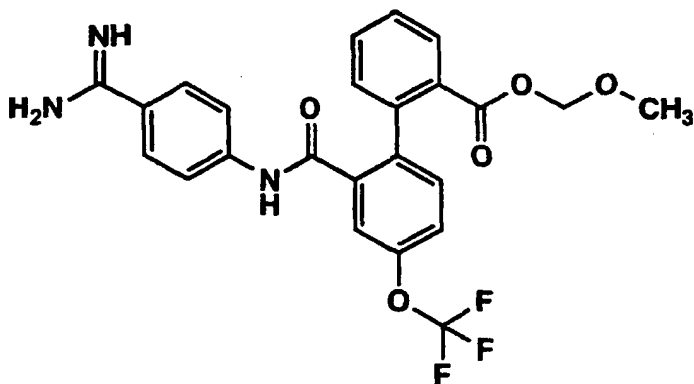
[0264]

35

40

45

50



55 TLC : Rf 0.31 (Chloroform : Methanol : Water = 8 : 2 : 0.1) ;
 NMR (CD_3OD) : δ 7.95 (1H, dd, J = 2.0, 7.4 Hz), 7.74-7.14 (10H, m), 5.25 (2H, s), 3.29 (3H, s).

Example 9(25)

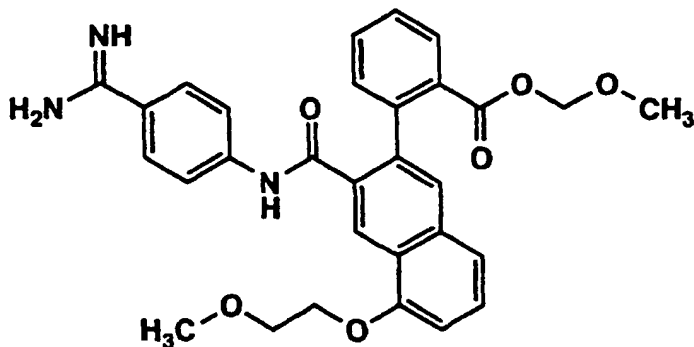
Methoxymethyl 2-(3-(4-amidinophenylcarbamoyl)-5-(2-methoxyethoxy) naphthalen-2-yl)benzoate

5 [0265]

10

15

20



25 TLC : Rf 0.45 (Chloroform : Methanol : Water = 10 : 3 : 0.2) ;
 NMR (d_6 -DMSO) : δ 10.77 (1H, s), 9.3-9.0 (3H, s), 8.40 (1H, s), 8.0-7.7 (6H, m), 7.7-7.4 (5H, m), 7.12 (1H, m), 5.09 (2H, br.s), 4.35 (2H, t, J = 5.0 Hz), 3.83 (2H, t, J = 5.0 Hz), 3.36 (3H, s), 3.06 (3H, s).

Example 9(26)

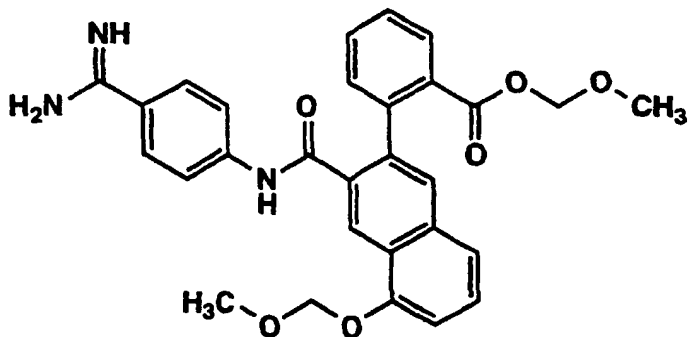
30 Methoxymethyl 2-(3-(4-amidinophenylcarbamoyl)-5-methoxymethoxy naphthalen-2-yl)benzoate

[0266]

35

40

45



50

55 TLC : Rf 0.57 (Chloroform : Methanol : Water = 10 : 3 : 0.2) ;
 NMR (d_6 -DMSO) : δ 10.81 (1H, s), 9.3-9.0 (3H, br), 8.44 (1H, s), 7.78 (4H, like s), 8.0-7.6 (3H, m), 7.7-7.4 (3H, m), 7.42 (1H, br.d, J = 7.8 Hz), 7.22 (1H, br.d, J = 6.4 Hz), 5.49 (2H, s), 5.09 (2H, br.s), 3.49 (3H, s), 3.05 (3H, s).

55

Example 9(27)

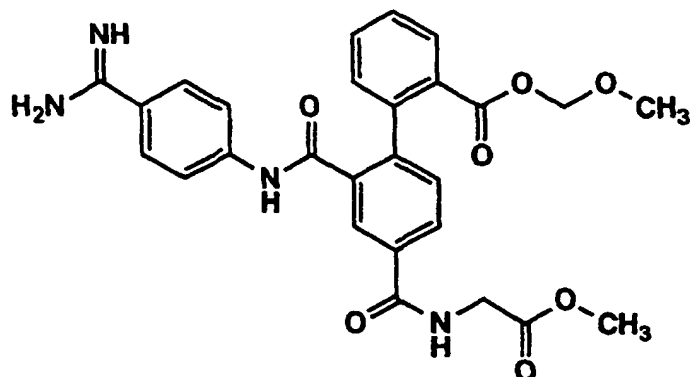
Methoxymethyl 2'-(4-amidinophenylcarbamoyl)-4'-((methoxycarbonylmethyl) carbamoyl)-2-biphenylcarboxylate

5 [0267]

10

15

20



25

TLC : Rf 0.21 (Chloroform : Methanol : Water = 8 : 2 : 0.2) ;
 NMR (CD₃OD) : δ 8.20 (1H, d, J = 1.8 Hz), 8.06 (1H, dd, J = 1.8, 7.8 Hz), 7.97 (1H, dd, J = 1.8, 7.8 Hz), 7.72 (2H, d, J = 9.2 Hz), 7.67 (2H, d, J = 9.2 Hz), 7.61 (1H, dt, J = 1.8, 7.8 Hz), 7.48 (1H, dt, J = 1.8, 7.8 Hz), 7.44 (1H, d, J = 7.8 Hz), 7.37 (1H, dd, J = 1.8, 7.8 Hz), 5.23 (2H, s), 4.18 (2H, s), 3.77 (3H, s), 3.27 (3H, s).

30 Example 9(28)

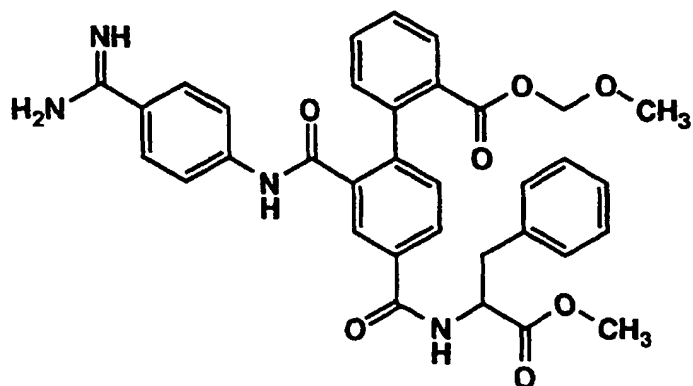
Methoxymethyl 2'-(4-amidinophenylcarbamoyl)-4'-((1-methoxycarbonyl-2-phenylethyl)carbamoyl)-2-biphenylcarboxylate

35 [0268]

40

45

50



55

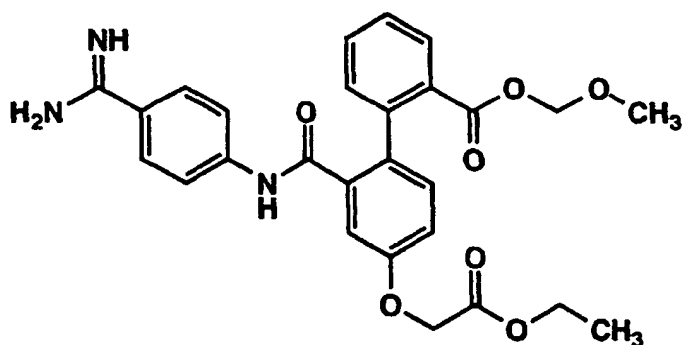
TLC : Rf 0.37 (Chloroform : Methanol : Water = 8 : 2 : 0.2) ;
 NMR (CD₃OD) : δ 8.06 (1H, d, J = 1.6 Hz), 7.95 (1H, dd, J = 1.6, 7.6 Hz), 7.94 (1H, dd, J = 1.6, 7.6 Hz), 7.72 (2H,

d, J = 9.0 Hz), 7.66 (2H, d, J = 9.0 Hz), 7.60 (1H, dt, J = 1.6, 7.6 Hz), 7.46 (1H, dt, J = 1.6, 7.6 Hz), 7.39 (1H, d, J = 7.6 Hz), 7.35 (1H, dd, J = 1.6, 7.6 Hz), 7.20-7.29 (5H, m), 5.22 (2H, s), 4.92 (1H, m), 3.75 (3H, s), 3.23 (3H, s), 3.09-3.39 (2H, m).

5 Example 9(29)

Methoxymethyl 2'-(4-amidinophenylcarbamoyl)-4'-ethoxycarbonylmethoxy-2-biphenylcarboxylate

[0269]



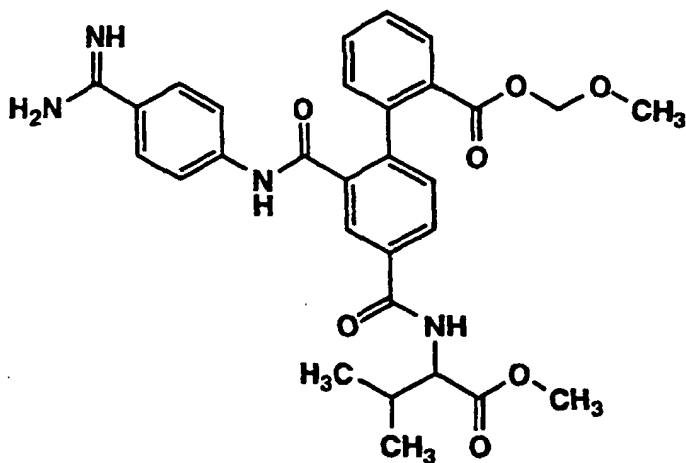
TLC : Rf 0.50 (Chloroform : Methanol : Water = 10 : 3 : 0.2) ;

NMR (d_6 -DMSO) : δ 10.51 (1H, s), 9.3-8.9 (3H, br), 7.9-7.6 (5H, m), 7.57 (1H, dt, J = 1.4, 7.4 Hz), 7.42 (1H, dt, J = 1.4, 7.4 Hz), 7.4-7.1 (3H, m), 7.12 (1H, dd, J = 2.6, 8.4 Hz), 5.11 (2H, s), 4.91 (2H, s), 4.19 (2H, q, J = 7.4 Hz), 3.14 (3H, s), 1.22 (3H, t, J = 7.4 Hz).

Example 9(30)

Methoxymethyl 2'-((4-amidinophenylcarbamoyl)-4'-((1-methoxycarbonyl-2-methylpropyl)carbamoyl)-2-biphenylcarboxylate

[0270]



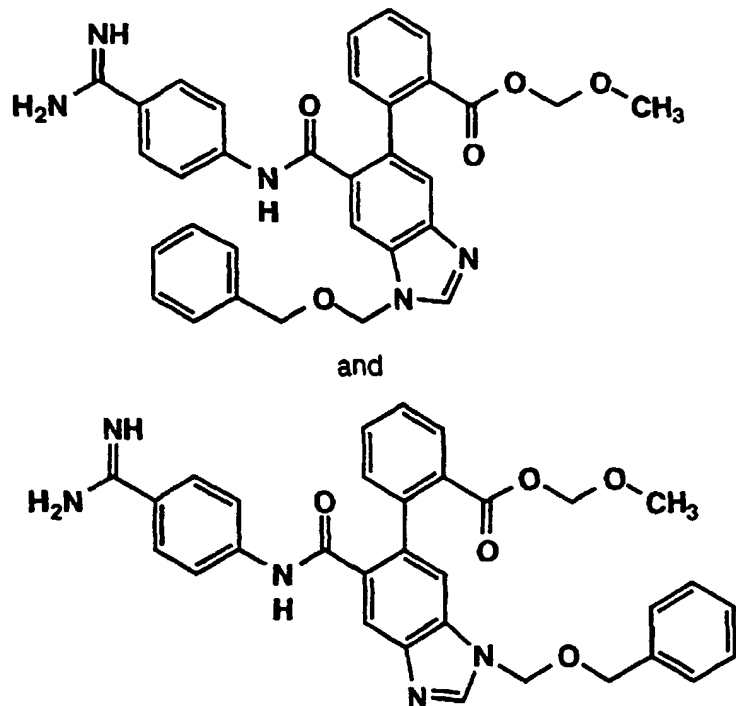
TLC : Rf 0.33 (Chloroform : Methanol : Water = 8 : 2 : 0.2) ;

NMR (CD₃OD) : δ 8.18 (1H, d, J = 1.8 Hz), 8.06 (1H, dd, J = 1.8, 7.8 Hz), 7.97 (1H, dd, J = 1.8, 7.8 Hz), 7.73 (2H, d, J = 9.2 Hz), 7.67 (2H, d, J = 9.2 Hz), 7.61 (1H, dt, J = 1.8, 7.8 Hz), 7.48 (1H, dt, J = 1.8, 7.8 Hz), 7.43 (1H, d, J = 7.8 Hz), 7.36 (1H, dd, J = 1.8, 7.8 Hz), 5.25 (2H, s), 4.56 (1H, m), 3.78 (3H, s), 3.29 (3H, s), 2.30 (1H, m), 1.06 (3H, d, J = 6.8 Hz), 1.04 (3H, d, J = 6.8 Hz).

Example 9(31)

A mixture of Methoxymethyl 2-(6-(4-amidinophenylcarbamoyl)-1-benzyloxymethylbenzoimidazol-5-yl)benzoate and Methoxymethyl 2-(5-(4-amidinophenylcarbamoyl)-1-benzyloxymethylbenzoimidazol-6-yl)benzoate

[0271]



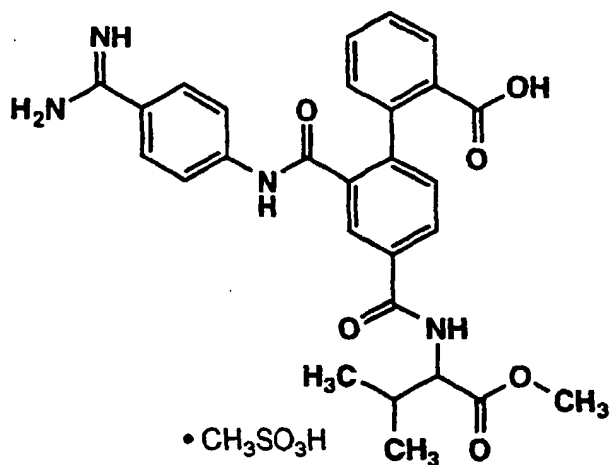
TLC : Rf 0.23 (Chloroform : Methanol : Water = 8 : 2 : 0.2) ;

NMR (CD₃OD) : δ 8.46 (0.5H, s), 8.43 (0.5H, s), 8.03 (0.5H, s), 7.98 (0.5H, s), 7.93 (0.5H, dd, J = 1.2, 7.5 Hz), 7.90 (0.5H, dd, J = 1.2, 7.5 Hz), 7.71 (1H, d, J = 9.0 Hz), 7.70 (1H, d, J = 9.0 Hz), 7.66 (1H, d, J = 9.0 Hz), 7.63 (1H, d, J = 9.0 Hz), 7.59 (0.5H, dt, J = 1.2, 7.5 Hz), 7.58 (0.5H, dt, J = 1.2, 7.5 Hz), 7.57 (0.5H, s), 7.52 (0.5H, s), 7.46 (0.5H, dt, J = 1.2, 7.5 Hz), 7.44 (0.5H, dt, J = 1.2, 7.5 Hz), 7.41 (0.5H, dd, J = 1.2, 7.5 Hz), 7.40 (0.5H, dd, J = 1.2, 7.5 Hz), 7.30 (2.5H, s), 7.25 (2.5H, s), 5.85 (1H, s), 5.78 (1H, s), 5.24 (1H, br.s), 5.18 (1H, br.s), 4.60 (1H, s), 4.55 (1H, s), 3.22 (1.5H, s), 3.15 (1.5H, s).

Example 10

2'-(4-amidinophenylcarbamoyl)-4'-((1-methoxycarbonyl-2-methylpropyl)carbamoyl)-2-biphenylcarboxylic acid methanesulfonate

[0272]



[0273] The present compound having the following physical data was obtained by the same procedure as a series of reaction of Example 4, using a compound prepared in Example 9(30).

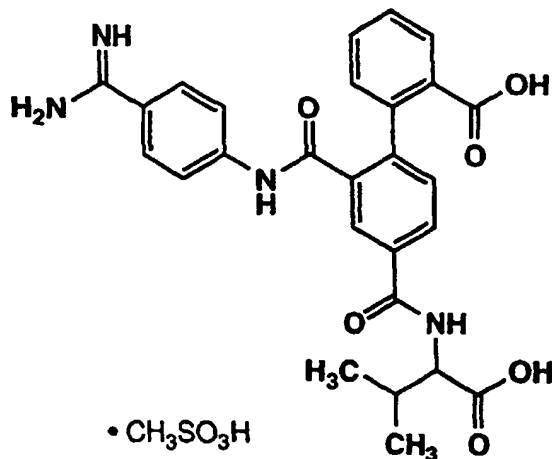
TLC : R_f 0.42 (Chloroform : Methanol : Water = 7 : 3 : 0.3) ;

NMR (CD₃OD) : δ 8.17 (1H, d, J = 1.8 Hz), 8.02 (1H, dd, J = 1.8, 7.8 Hz), 7.92 (1H, dd, J = 1.8, 7.8 Hz), 7.71 (2H, d, J = 9.2 Hz), 7.62 (2H, d, J = 9.2 Hz), 7.54 (1H, dt, J = 1.8, 7.8 Hz), 7.44 (1H, dt, J = 1.8, 7.8 Hz), 7.36 (1H, d, J = 7.8 Hz), 7.28 (1H, dd, J = 1.8, 7.8 Hz), 4.55 (1H, d, J = 6.4 Hz), 3.77 (3H, s), 2.70 (3H, s), 2.29 (1H, m), 1.06 (3H, d, J = 6.4 Hz), 1.04 (3H, d, J = 6.4 Hz).

Example 11

2'-(4-amidinophenylcarbamoyl)-4'-((1-carboxy-2-methylpropyl)carbamoyl)-2-biphenylcarboxylic acid methanesulfonate

[0274]



[0275] 2N aqueous solution of sodium hydroxide (1.5 ml) was added to a solution of the compound prepared in Example 10 (710 mg) in methanol (10 ml). The mixture was stirred for 12 hours at room temperature. 2N hydrochloric acid was added to the reaction mixture, and the solution was concentrated. The residue was purified by column chromatography on silica gel (Chloroform : Methanol : Water = 7 : 3 : 0.3 → Trifluoroacetic acid : dimethylformamide = 1 : 99). 1N methanesulfonic acid (1.0 ml) was added to the purified compound to give the present compound (652 mg) having the following physical data.

TLC : R_f 0.11 (Chloroform : Methanol : Water = 7 : 3 : 0.3) ;

NMR (d₆-DMSO) : δ 10.69 (1H, s), 9.26 (2H, s), 9.05 (2H, s), 8.67 (1H, d, J = 8.2 Hz), 8.25 (1H, s), 8.05 (1H, dd, J = 1.8, 8.0 Hz), 7.88 (1H, dd, J = 1.8, 8.0 Hz), 7.79 (2H, d, J = 9.2 Hz), 7.75 (2H, d, J = 9.2 Hz), 7.55 (1H, dt, J = 1.8, 8.0 Hz), 7.44 (1H, dt, J = 1.8, 8.0 Hz), 7.35 (1H, d, J = 8.0 Hz), 7.25 (1H, dd, J = 1.8, 8.0 Hz), 4.36 (1H, m), 2.37 (3H, s), 2.25 (1H, m), 1.02 (3H, d, J = 6.8 Hz), 1.00 (3H, d, J = 6.8 Hz).

Reference Example 9

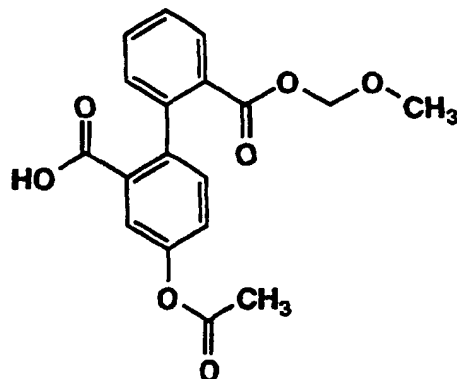
2'-methoxymethoxycarbonyl-4-acetoxy-2-biphenylcarboxylic acid

5 [0276]

10

15

20



25 [0277] 2'-methoxymethoxycarbonyl-4-hydroxy-2-biphenylcarboxylic acid (606 mg) which was prepared by the same procedure as a series of reaction of Reference Example 4 → Reference Example 5 → Reference Example 6 → Example 2 (without a procedure of conversion to salt thereof), using benzyl 2-trifluoromethylsulfonyloxy-5-benzyloxybenzoate, was dissolved into acetic acid anhydrous (1 ml) and pyridine (2 ml). The solution was stirred for 12 hours at room temperature. Water (100 ml) was added to the reaction mixture, and the solution was extracted with ethyl acetate (2 times). The extract was washed with a saturated aqueous solution of ammonium chloride, a saturated aqueous solution of sodium chloride, dried over anhydrous magnesium sulfate and concentrated to give the title compound (700 mg) having the following physical data.

30 TLC : Rf 0.31 (Chloroform : Methanol : Water = 9 : 1 : 0.1) ;
 35 NMR (CDCl₃) : δ 8.06 (1H, dd, J = 1.4, 7.6 Hz), 7.82 (1H, d, J = 2.8 Hz), 7.55 (1H, dt, J = 1.4, 7.6 Hz), 7.44 (1H, dt, J = 1.4, 7.6 Hz), 7.19-7.36 (3H, m), 5.24 (1H, d, J = 6.2 Hz), 5.14 (1H, d, J = 6.2 Hz), 3.22 (3H, s), 2.33 (3H, s).

Reference Example 9(1)

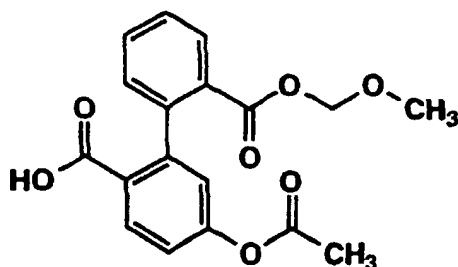
2'-methoxymethoxycarbonyl-5-acetoxy-2-biphenylcarboxylic acid

40

[0278]

45

50



55

[0279] The title compound having the following physical data was prepared by the same procedure as a series of reaction of Reference Example 9, using 2'-methoxymethoxycarbonyl-5-hydroxy-2-biphenylcarboxylic acid which was

prepared by the same procedure as a series of reaction of Reference Example 4 → Reference Example 5 → Reference Example 6 → Example 2 (without a procedure of conversion to salt thereof), using benzyl 2-trifluoromethylsulfonyloxy-4-benzyloxybenzoate.

5 TLC : Rf 0.38 (Chloroform : Methanol = 20 : 1) ;
 NMR (CDCl₃) : δ 8.11 (1H, d, J = 8.8 Hz), 8.06 (1H, dd, J = 1.4, 7.6 Hz), 7.54 (1H, dt, J = 1.4, 7.6 Hz), 7.44 (1H, dt, J = 1.4, 7.6 Hz), 7.23 (1H, dd, J = 1.4, 7.6 Hz), 7.19 (1H, dd, J = 2.2, 8.8 Hz), 6.98 (1H, d, J = 2.2 Hz), 5.22 (1H, d, J = 6.0 Hz), 5.18 (1H, d, J = 6.0 Hz), 3.24 (3H, s), 2.29 (3H, s).

10 Reference Example 10

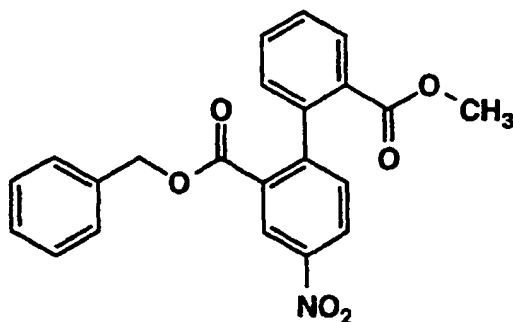
Methyl 2'-benzyloxycarbonyl-4'-nitro-2-biphenylcarboxylate

[0280]

15

20

25



30

[0281] To a solution of 2'-benzyloxycarbonyl-4'-nitro-2-biphenylcarboxylic acid (2.8 g) which was prepared by the same procedure as a series of reaction of Reference Example 4 → Reference Example 5, using Benzyl 2-trifluoromethylsulfonyloxy-5-nitrobenzoate, in ether-ethyl acetate (1 : 1, 40 ml), diazomethane (30 ml) was added. Acetic acid was added to the reaction mixture, and the solution was concentrated. The residue was purified by column chromatography on silica gel (hexane : ethyl acetate = 5 : 2) to give the title compound (2.57 g) having the following physical data.

35

TLC : Rf 0.51 (Hexane : Ethyl acetate = 5 : 2) ;
 NMR (CDCl₃) : δ 8.89 (1H, d, J = 2.2 Hz), 8.37 (1H, dd, J = 2.2, 8.4 Hz), 8.00 (1H, dd, J = 1.6, 7.6 Hz), 7.53 (1H, dt, J = 1.6, 7.6 Hz), 7.43 (1H, dt, J = 1.6, 7.6 Hz), 7.37 (1H, d, J = 8.4 Hz), 7.27-7.32 (3H, m), 7.12-7.16 (3H, m), 5.09 (2H, s), 3.60 (3H, s).

40

45

50

55

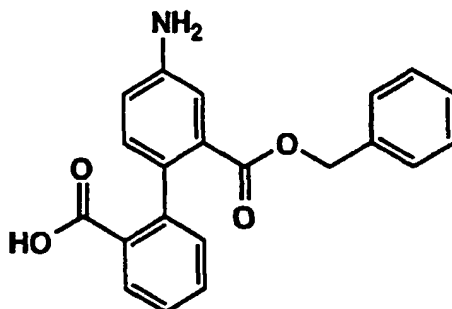
Reference Example 11

2'-benzyloxycarbonyl-4'-amino-2-biphenylcarboxylic acid

5 [0282]

10

15



20

[0283] To a solution of 2'-benzyloxycarbonyl-4'-nitro-2-biphenylcarboxylic acid (2.08 g) which was prepared by the same procedure as a series of reaction of Reference Example 4 → Reference Example 5, using Benzyl 2-trifluoromethylsulfonyloxy-5-nitrobenzoate, in concentration hydrochloric acid - ethanol (5 : 3, 8 ml), a solution of Tin (II) chloride dihydrate (3.7 g) in ethanol (5 ml) was added. The mixture was stirred for 1 hour at room temperature. 2N aqueous solution of sodium hydroxide was added to the reaction solution, the solution was extracted with ethyl acetate (2 times). The extract was washed with water, dried over anhydrous magnesium sulfate and concentrated. The residue was purified by column chromatography on silica gel (Chloroform : Methanol : Water = 9 : 1 : 0.1 → 8 : 2 : 0.2) to give the title compound (1.07 g) having the following physical data.

30

TLC : Rf 0.57 (Chloroform : Methanol : Water = 8 : 2 : 0.2) ;

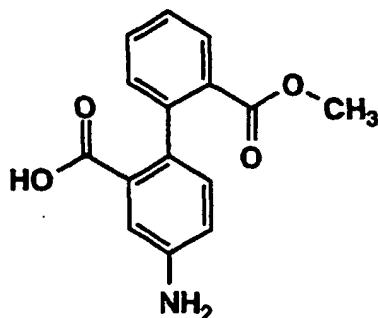
NMR (CDCl₃) : δ 7.86 (1H, dd, J = 1.8, 7.8 Hz), 7.42 (1H, dt, J = 1.8, 7.8 Hz), 7.31 (1H, dt, J = 1.8, 7.8 Hz), 7.24-7.27 (4H, m), 7.06-7.15 (3H, m), 6.95 (1H, d, J = 7.8 Hz), 6.77 (1H, dd, J = 1.8, 7.8 Hz), 5.03 (2H, s).

35 Reference Example 12

2'-methoxycarbonyl-4'-amino-2-biphenylcarboxylic acid

40 [0284]

45



50

55

[0285] To a mixed solution of the compound prepared in Reference Example 10 (2.5 g) in methanol-ethyl acetate (4 : 1, 10 ml), 20% palladium hydroxide on carbon (160 mg) was added. The mixture was stirred for 1 hour under an atmosphere of hydrogen gas. The reaction mixture was filtered through celite (registered trade mark). The filtrate was

concentrated. The residue was purified by column chromatography on silica gel (Chloroform : Methanol : Water = 9 : 1 : 0.1 → 7 : 3 : 0.3) to give the title compound (1.15 g) having the following physical data.

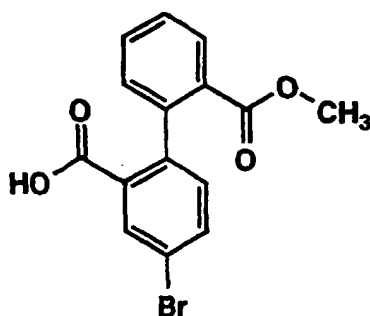
TLC : Rf 0.24 (Chloroform : Methanol : Water = 9 : 1 : 0.1) ;

NMR (CD₃OD) : δ 7.82 (1H, dd, J = 1.4, 7.6 Hz), 7.49 (1H, dt, J = 1.4, 7.6 Hz), 7.34 (1H, dt, J = 1.4, 7.6 Hz), 7.27 (1H, d, J = 2.0 Hz), 7.23 (1H, dd, J = 1.4, 7.6 Hz), 6.89 (1H, d, J = 8.0 Hz), 6.85 (1H, dd, J = 2.0, 8.0 Hz), 3.59 (3H, s).

Reference Example 13

2'-methoxycarbonyl-4-bromo-2-biphenylcarboxylic acid

[0286]



[0287] To a solution of the compound prepared in Reference Example 12 (550 mg) in 48 % aqueous solution of hydrogen bromide (2.7 ml), an aqueous solution (1.4 ml) of sodium nitrate (140 mg) was added at 5 - 10 °C. Copper bromide (160 mg) was added to the reaction mixture, and the mixture was stirred for 30 minutes at 50 °C. Water (50 ml) was added to the reaction mixture, and the solution was extracted with ethyl acetate. The extract was washed with water, dried over anhydrous magnesium sulfate and concentrated. The residue was washed with hexane to give the title compound (585 mg) having the following physical data.

TLC : Rf 0.63 (Chloroform : Methanol : Water = 9 : 1 : 0.1) ;

NMR (CDCl₃) : δ 8.16 (1H, d, J = 2.2 Hz), 8.00 (1H, dd, J = 1.8, 7.4 Hz), 7.67 (1H, dd, J = 2.2, 8.4 Hz), 7.54 (1H, dt, J = 1.8, 7.4 Hz), 7.44 (1H, dt, J = 1.8, 7.4 Hz), 7.16 (1H, dd, J = 1.8, 7.4 Hz), 7.05 (1H, d, J = 8.4 Hz), 3.67 (3H, s).

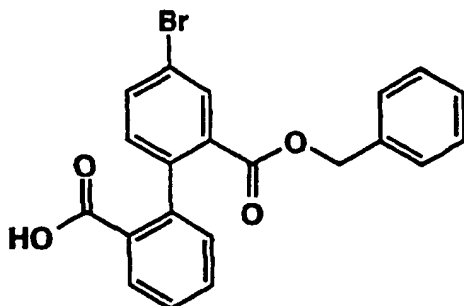
Reference Example 13(1)

2'-benzyloxycarbonyl-4'-bromo-2-biphenylcarboxylic acid

5 [0288]

10

15



20

[0289] The title compound was obtained by the same procedure as a series of reaction of Reference Example 13, using the compound prepared in Reference Example 11.

25 TLC : Rf 0.48 (Chloroform : Methanol : Water = 9 : 1 : 0.1) ;
 NMR (CDCl₃) : δ 8.15 (1H, d, J = 2.2 Hz), 7.96 (1H, dd, J = 1.6, 7.8 Hz), 7.61 (1H, dd, J = 2.2, 8.2 Hz), 7.48 (1H, dt, J = 1.6, 7.8 Hz), 7.36 (1H, dt, J = 1.6, 7.8 Hz), 7.24-7.27 (3H, m), 7.08-7.13 (3H, m), 7.03 (1H, d, J = 8.2 Hz), 5.02 (2H, s).

30 Example 12 — Example 12(3)

[0290] The following compounds were obtained by the same procedure as a series of reaction of Example 1, using the compound prepared in Reference Example 9 — Reference Example 9(1), and Reference Example 13 — Reference Example 13(1).

35

Example 12

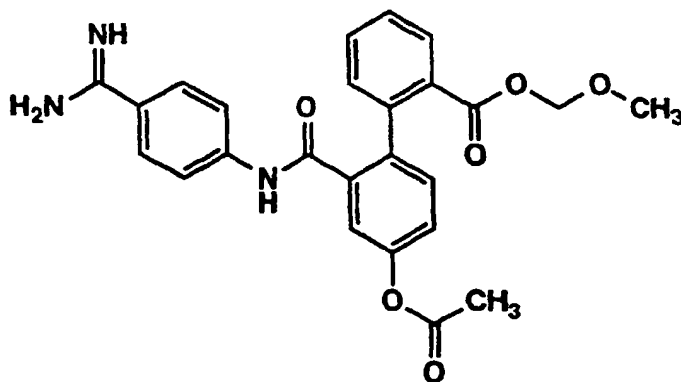
Methoxymethyl 2'-(4-amidinophenylcarbamoyl)-4'-acetoxo-2-biphenyl carboxylate

40 [0291]

45

50

55



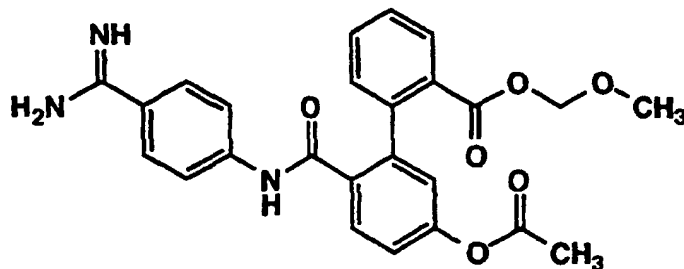
TLC : Rf 0.40 (Chloroform : Methanol : Water = 8 : 2 : 0.2) ;

NMR (CD₃OD) : δ 7.92 (1H, dd, J = 1.4, 7.6 Hz), 7.71 (2H, d, J = 9.0 Hz), 7.62 (2H, d, J = 9.0 Hz), 7.57 (1H, dd, J = 1.4, 7.6 Hz), 7.34-7.49 (5H, m), 5.24 (2H, br.s), 3.26 (3H, s), 2.33 (3H, s).

Example 12(1)

Methoxymethyl 2'-(4-amidinophenylcarbamoyl)-5'-acetoxy-2-biphenyl carboxylate

[0292]



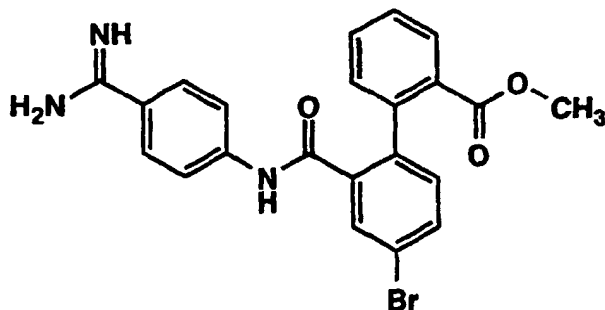
TLC : Rf 0.25 (Chloroform : Methanol : Water = 8 : 2 : 0.2) ;

NMR (CD₃OD) : δ 7.92 (1H, dd, J = 1.4, 7.8 Hz), 7.61-7.74 (5H, m), 7.57 (1H, dt, J = 1.4, 7.8 Hz), 7.45 (1H, dt, J = 1.4, 7.8 Hz), 7.35 (1H, dd, J = 1.4, 7.8 Hz), 7.27 (1H, dd, J = 2.4, 8.4 Hz), 7.08 (1H, d, J = 2.4 Hz), 5.25 (2H, s), 3.27 (3H, s), 2.30 (3H, s).

Example 12(2)

Methoxymethyl 2'-(4-amidinophenylcarbamoyl)-4'-bromo-2-biphenylcarboxylate

[0293]



TLC : Rf 0.25 (Chloroform : Methanol : Water = 8 : 2 : 0.2) ;

NMR (CD₃OD) : δ 7.85 (1H, dd, J = 1.4, 7.8 Hz), 7.82 (1H, d, J = 2.2 Hz), 7.72 (1H, dd, J = 2.2, 8.4 Hz), 7.71 (2H, d, J = 9.2 Hz), 7.63 (2H, d, J = 9.2 Hz), 7.56 (1H, dt, J = 1.4, 7.8 Hz), 7.43 (1H, dt, J = 1.4, 7.8 Hz), 7.34 (1H, dd, J

= 1.4, 7.8 Hz), 7.21 (1H, d, J = 8.4 Hz), 3.69 (3H, s).

Example 12(3)

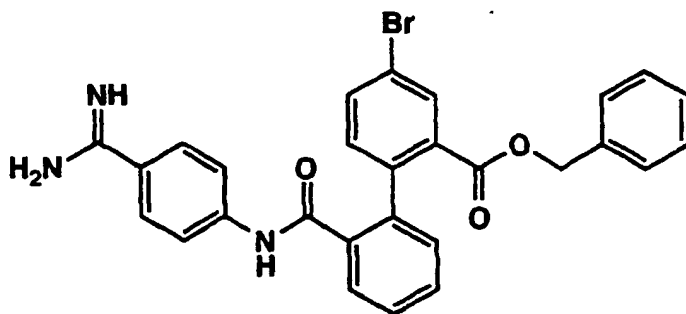
5 Benzyl 2'-(4-amidinophenylcarbamoyl)-4-bromo-2-biphenylcarboxylate

[0294]

10

15

20



25

TLC : Rf 0.25 (Chloroform : Methanol : Water = 8 : 2 : 0.2) ;
NMR (CD₃OD) : δ 7.97 (1H, d, J = 2.2 Hz), 7.60-7.73 (6H, m), 7.48-7.53 (2H, m), 7.22-7.29 (5H, m), 7.10-7.15 (2H, m), 5.10 (2H, s).

Example 13

30

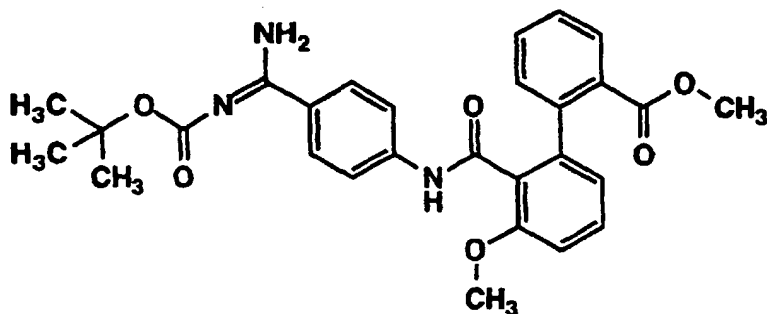
Methyl 2'-(4-(N²-t-butoxycarbonylamidino)phenylcarbamoyl)-3'-methoxy-2-biphenylcarboxylate

[0295]

35

40

45



50 [0296] The present compound having the following physical data was obtained by the same procedure as a series of reaction of Reference Example 4 → Reference Example 5 → Reference Example 10 → Reference Example 12 → Reference Example 3, using benzyl 2-trifluoromethylsulfonyloxy-6-methoxybenzoate.

55

TLC : Rf 0.63 (Chloroform : Methanol : Water = 9 : 1 : 0.1) ;
NMR (CDCl₃) : δ 8.81 (1H, s), 7.67-7.75 (1H, m), 7.68 (2H, d, J = 8.6 Hz), 7.28-7.46 (4H, m), 7.33 (2H, d, J = 8.6 Hz), 6.99 (1H, d, J = 8.4 Hz), 6.69 (1H, d, J = 7.6 Hz), 3.92 (3H, s), 3.84 (3H, s), 1.53 (9H, s).

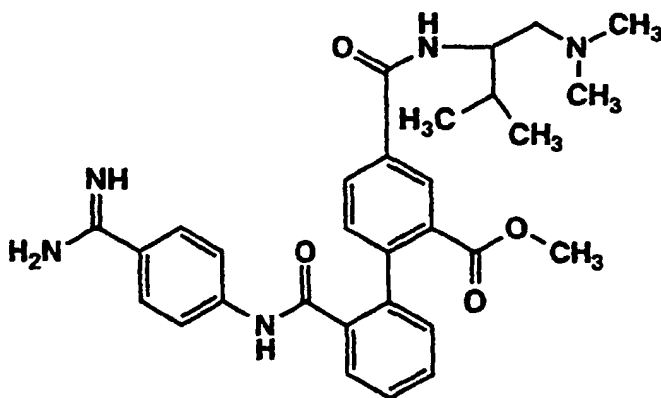
Example 14 — Example 14(2)

[0297] The following compounds having the following physical data were obtained by the same procedure as a series of reaction of Reference Example 4 → Reference Example 5 → Reference Example 7 → Reference Example 8 → Reference Example 5 → Reference Example 3 (using a corresponding derivative instead of 2, 2-dimethylpropylamine) → Example 2 → Example 1, using methyl 5-(1,3-dioxoran-2-yl)-2-trifluoromethylsulfonyloxybenzoate.

Example 14

Methyl 2'-(4-amidinophenylcarbamoyl)-4-((1-dimethylaminomethyl-2-methylpropyl)carbamoyl)-2-biphenylcarboxylate

[0298]



TLC : Rf 0.28 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d_6 -DMSO) : δ 10.72 (1H, s), 9.35-9.1 (3H, br), 8.73 (1H, d, J = 9.4 Hz), 8.29 (1H, s), 8.19 (1H, d, J = 7.8 Hz), 7.78 (4H, like s), 7.71 (1H, d, J = 7.8 Hz), 7.7-7.5 (2H, m), 7.42 (1H, d, J = 7.8 Hz), 7.29 (1H, d, J = 7.8 Hz), 4.21 (1H, br), 3.54 (3H, s), 3.6-3.2 (2H, br), 2.78 (3H, s), 2.77 (3H, s), 1.84 (1H, m), 0.92 (3H, d, J = 7.4 Hz), 0.88 (3H, d, J = 7.4 Hz).

Example 14(1)

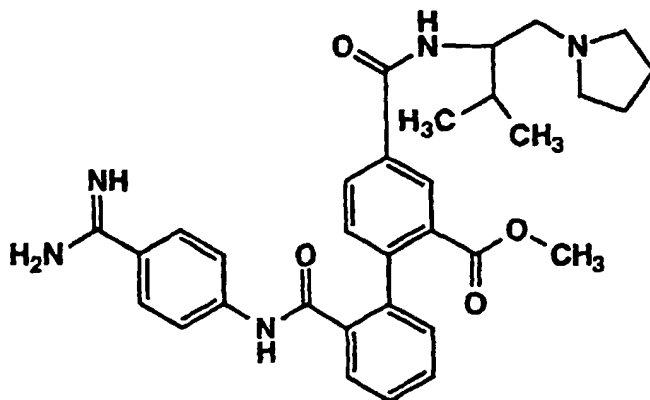
Methyl 2'-[4-amidinophenylcarbamoyl]-4-[(1-(pyrrolidin-1-ylmethyl)-2-methylpropyl)carbamoyl]-2-biphenylcarboxylate

5 [0299]

10

15

20



25

TLC : Rf 0.28 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d₆-DMSO) : δ 10.73 (1H, s), 9.4-9.1 (3H, br), 8.73 (1H, d, J = 7.4 Hz), 8.30 (1H, d, J = 2.0 Hz), 8.20 (1H, dd, J = 2.0, 8.0 Hz), 7.9-7.6 (5H, m), 7.7-7.5 (2H, m), 7.41 (1H, d, J = 8.0 Hz), 7.29 (1H, dd, J = 2.0, 8.0 Hz), 4.17 (1H, br), 3.54 (3H, s), 3.6-3.3 (4H, br), 3.2-3.0 (2H, br), 2.0-1.7 (5H, m), 0.92 (3H, d, J = 8.0 Hz), 0.88 (3H, d, J = 8.0 Hz).

30

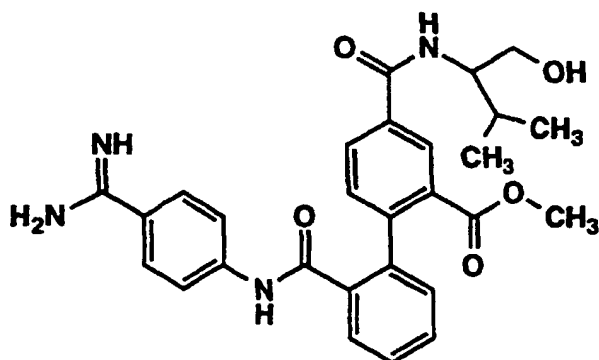
Example 14(2)

Methyl 2'-[4-amidinophenylcarbamoyl]-4-[(1-hydroxymethyl-2-methylpropyl)carbamoyl]-2-biphenylcarboxylate

35 [0300]

40

45



50

TLC : Rf 0.49 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

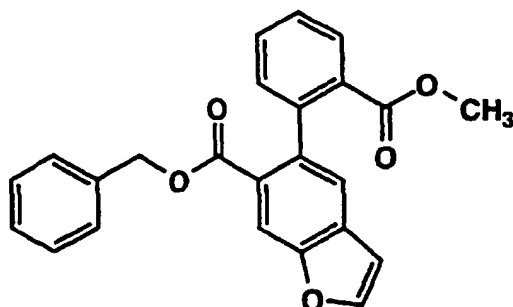
55

NMR (d₆-DMSO) : δ 10.62 (1H, br.s), 9.11 (3H, s), 8.25 (1H, s), 8.21 (1H, br), 8.06 (1H, dd, J = 1.5, 7.8 Hz), 7.75 (4H, like s), 7.69 (1H, br.d, J = 7.2 Hz), 7.60 (1H, dt, J = 1.5, 7.2 Hz), 7.54 (1H, dt, J = 1.5, 7.2 Hz), 7.40 (1H, d, J = 7.8 Hz), 7.31 (1H, br.d, J = 7.2 Hz), 4.60 (1H, br), 4.09 (1H, br), 3.81 (1H, m), 3.54 (3H, s), 3.51 (1H, m), 1.91 (1H, like sextet, J = 6.6 Hz), 0.90 (3H, d, J = 7.0 Hz), 0.87 (3H, d, J = 7.0 Hz).

Reference Example 14

Methyl 2-(6-benzyloxycarbonylbenzofuran-5-yl)benzoate

[0301]



[0302] To a solution of 2-(6-benzyloxycarbonylbenzofuran-5-yl)benzoic acid (1.12 g) which was prepared by the same procedure as a series of reaction of Reference Example 4 → Reference Example 5, using benzyl 5-trifluoromethylsulfonyloxy-6-benzofurancarboxylate, in dimethylformamide (12 ml), methyl iodide (205 μ l) and potassium carbonate (455 mg) was added. The mixture was stirred for 14 hours at room temperature. Water was added to the reaction mixture, and the solution was extracted with ethyl acetate. The extract was washed with water and a saturated aqueous solution of sodium chloride, dried over anhydrous sodium sulfate and concentrated to give the title compound (1.16 g) having the following physical data.

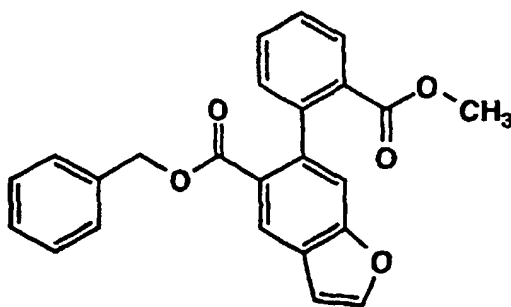
TLC : Rf 0.49 (Hexane : Ethyl acetate = 8 : 2) ;

NMR (CDCl_3) : δ 8.24 (1H, d, J = 1.0 Hz), 7.93 (1H, dd, J = 8.0, 1.5 Hz), 7.77 (1H, d, J = 2.0 Hz), 7.49 (1H, td, J = 8.0, 1.5 Hz), 7.38 (1H, s), 7.37 (1H, td, J = 8.0, 1.5 Hz), 7.32-7.14 (6H, m), 6.79 (1H, dd, J = 2.0, 1.0 Hz), 5.09 (2H, s), 3.55 (3H, s).

Reference Example 14(1)

Methyl 2-(5-benzyloxycarbonylbenzofuran-6-yl)benzoate

[0303]



[0304] The title compound having the following physical data was obtained by the same procedure as a series of reaction of Reference Example 14, using 2-(5-benzyloxycarbonylbenzofuran-6-yl)benzoic acid.

TLC : Rf 0.50 (Hexane : Ethyl acetate = 8 : 2) ;

NMR (CDCl_3) : δ 8.35 (1H, s), 7.94 (1H, dd, J = 8.0, 1.5 Hz), 7.68 (1H, d, J = 2.0 Hz), 7.50 (1H, td, J = 8.0, 1.5 Hz),

7.37 (1H, td, J = 8.0, 1.5 Hz), 7.33-7.13 (7H, m), 6.85 (1H, dd, J = 2.0, 1.0 Hz), 5.07 (2H, s), 3.56 (3H, s).

Example 15 — Example 15(1)

- 5 [0305] The following compounds were obtained by the same procedure as a series of reaction of Example 2 → Example 1, using the compounds prepared in Reference Example 14 — Reference Example 14(1).

Example 15

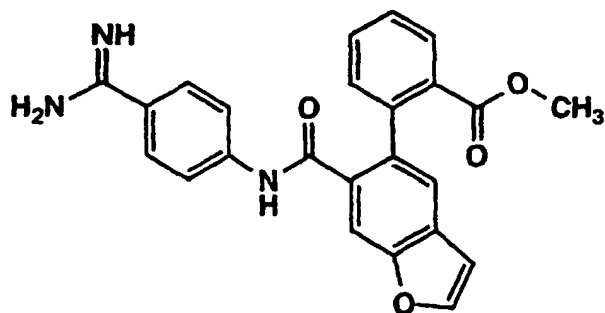
- 10 Methyl 2-(6-(4-amidinophenylcarbamoyl)benzofuran-5-yl)benzoate

[0306]

15

20

25



30

TLC : Rf 0.60 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;
NMR (CD₃OD) : δ 7.95 (1H, d, J = 2.0 Hz), 7.85 (1H, d, J = 1.0 Hz), 7.82 (1H, dd, J = 8.0 Hz, 1.5 Hz), 7.70 (2H, d, J = 9.0 Hz), 7.61 (2H, d, J = 9.0 Hz), 7.54 (1H, td, J = 8.0 Hz, 1.5 Hz), 7.50 (1H, s), 7.40 (1H, td, J = 8.0 Hz, 1.5 Hz), 7.37 (1H, dd, J = 8.0 Hz, 1.5 Hz), 6.94 (1H, dd, J = 2.0 Hz 1.0 Hz), 3.67 (3H, s).

- 35 Example 15(1)

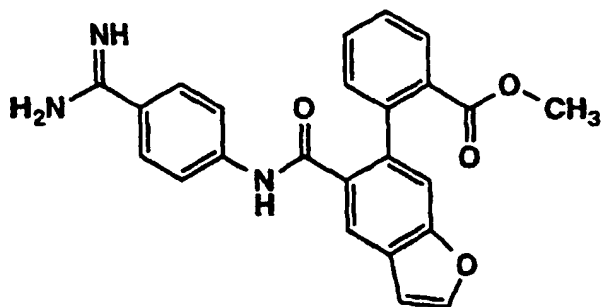
Methyl 2-(5-(4-amidinophenylcarbamoyl)benzofuran-6-yl)benzoate

[0307]

40

45

50



55

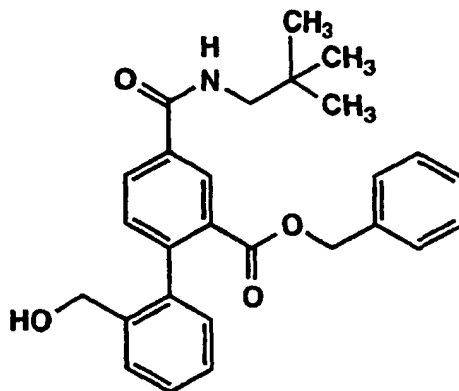
TLC : Rf 0.60 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;
NMR (CD₃OD) : δ 7.96 (1H, s), 7.90 (1H, d, J = 2.0 Hz), 7.83 (1H, dd, J = 8.0 Hz, 1.5 Hz), 7.70 (2H, d, J = 9.0 Hz), 7.61 (2H, d, J = 9.0 Hz), 7.54 (1H, td, J = 8.0 Hz, 1.5 Hz), 7.40 (1H, td, J = 8.0 Hz, 1.5 Hz), 7.40 (1H, d, J = 1.0 Hz),

7.38 (1H, dd, J = 8.0 Hz, 1.5 Hz), 7.00 (1H, dd, J = 2.0 Hz, 1.0 Hz), 3.67 (3H, s).

Reference Example 15

5 Benzyl 2'-hydroxymethyl-4-((2, 2-dimethylpropyl)carbamoyl)-2-biphenylcarboxylate

[0308]



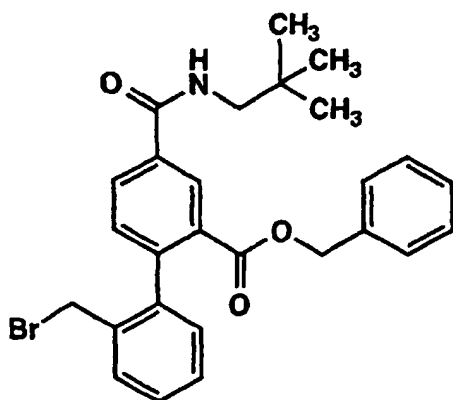
25 [0309] To a solution of the compound prepared in Reference Example 4 (1.65 g) in methanol (20 ml), sodium borohydride (174 mg) was added at -50 °C. The mixture was stirred for 15 minutes at -50 °C. Acetone was added to a reaction solution, and was diluted with ethyl acetate (80 ml). The solution was washed with a saturated aqueous solution of sodium chloride (40 ml, 2 times), dried over anhydrous sodium sulfate and concentrated to give the present compound

30 (1.65 g) having the following physical data.
TLC : Rf 0.40 (Hexane : Ethyl acetate = 1 : 1).

Reference Example 16

35 Benzyl 2'-bromomethyl-4-((2, 2-dimethylpropyl)carbamoyl)-2-biphenylcarboxylate

[0310]



55 [0311] A solution of the compound prepared in Reference Example 15 (1.65 g) in methylene chloride (15 ml), carbon tetrabromide (2.55 g) and triphenylphosphine (1.51 g) were added at 0 °C. The mixture was stirred for 15 minutes

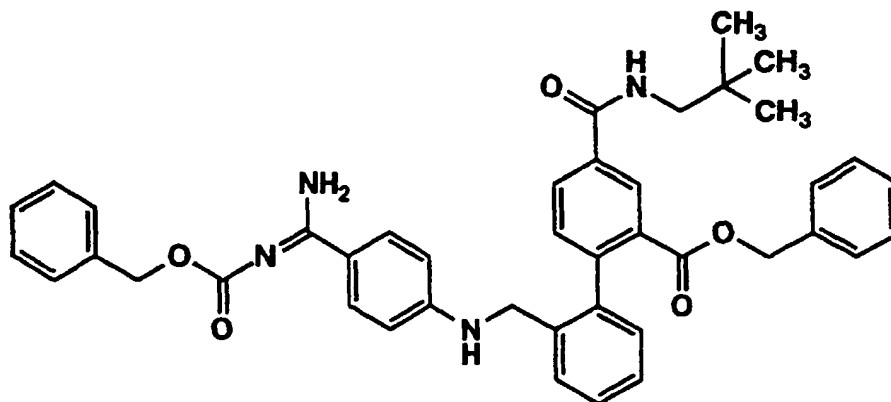
at room temperature. A saturated aqueous solution of sodium bicarbonate (50 ml) was added to the mixture, and the solution was extracted with ethyl acetate (50 ml, 2 times). The extract was washed with a saturated aqueous solution of sodium chloride (100 ml), dried over anhydrous sodium sulfate and concentrated. The residue was purified by column chromatography on silica gel (hexane : ethyl acetate = 3 : 1) to give the title compound (1.45 g) having the following physical data.

TLC : Rf 0.56 (Hexane : Ethyl acetate = 1 : 1).

Example 16

Benzyl 2'-[4-(N²-benzyloxycarbonylamidino)phenylaminomethyl]-4-[(2, 2-dimethylpropyl)carbamoyl]-2-biphenylcarboxylate

[0312]



[0313] The compound prepared in Reference Example 16 (900 mg), potassium carbonate (301 mg), sodium iodide (273 mg) and 4-(N²-benzyloxycarbonylamidino)aniline (587 mg) were dissolved into dimethylformamide (20 ml). The mixture was stirred for 65 hours at room temperature. The reaction mixture was diluted with ethyl acetate (100 ml), and washed with a saturated aqueous solution of sodium chloride (150 ml; three times). The organic layer was dried over anhydrous sodium sulfate and concentrated. The residue was purified by column chromatography on silica gel (Chloroform : Ethyl acetate = 3 : 1). The obtained solid was washed with ether to give the present compound (667 mg) having the following physical data.

TLC : Rf 0.83 (Chloroform : Methanol = 10 : 1) ;

NMR (d₆-DMSO) : δ 9.4-8.4 (2H, br), 8.57 (1H, br), 8.37 (1H, d, J = 1.8 Hz), 8.09 (1H, dd, J = 1.8, 8.0 Hz), 7.72 (2H, d, J = 9.0 Hz), 7.49 (1H, d, J = 8.0 Hz), 7.4-7.2 (11H, m), 7.2-7.1 (2H, m), 7.05 (1H, d, J = 8.0 Hz), 6.57 (1H, br), 6.41 (2H, d, J = 9.0 Hz), 5.12 (2H, s), 5.05 (2H, s), 3.98 (2H, br.s), 3.12 (2H, d, J = 6.6 Hz), 0.90 (9H, s).

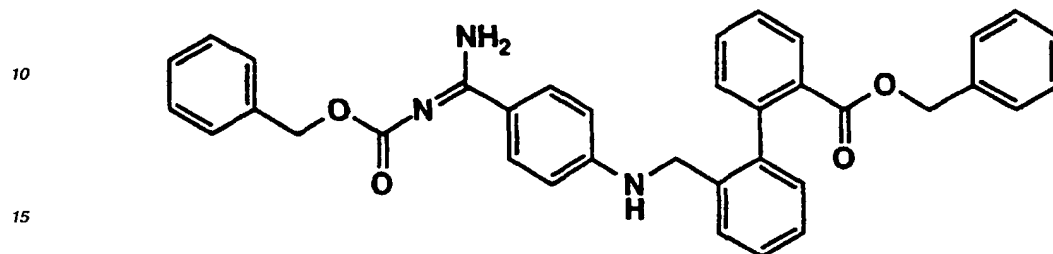
Example 17 — Example 17(10)

[0314] The following compounds were obtained by the same procedure as a series of reaction of Reference Example 15 → Reference Example 16 → Example 16, using a corresponding derivatives instead of the starting compound in Reference Example 15.

Example 17

Benzyl 2'-(4-(N²-benzyloxycarbonylamidino)phenylaminomethyl)-2-biphenylcarboxylate

5 [0315]



20

TLC : R_f 0.68 (Chloroform : Ethyl acetate = 8 : 2) ;

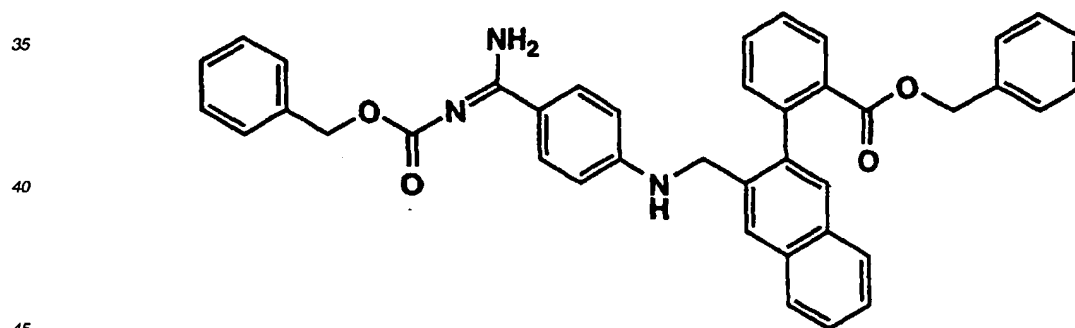
25 NMR (CDCl₃) : δ 9.7-9.2 (1H, broad), 7.95 (1H, dd, J = 8.0 Hz, 1.5 Hz), 7.62-7.05 (19H, m), 6.25 (2H, d, J = 9.0 Hz), 5.19 (2H, s), 5.13 (1H, d, J = 12 Hz), 5.03 (1H, d, J = 12 Hz), 4.37 (1H, t, J = 5.0 Hz), 4.04 (2H, d, J = 5.0 Hz).

Example 17(1)

Benzyl 2-(3-(4-(N²-benzyloxycarbonylamidino)phenylaminomethyl) naphthalen-2-yl)benzoate

30

[0316]



50

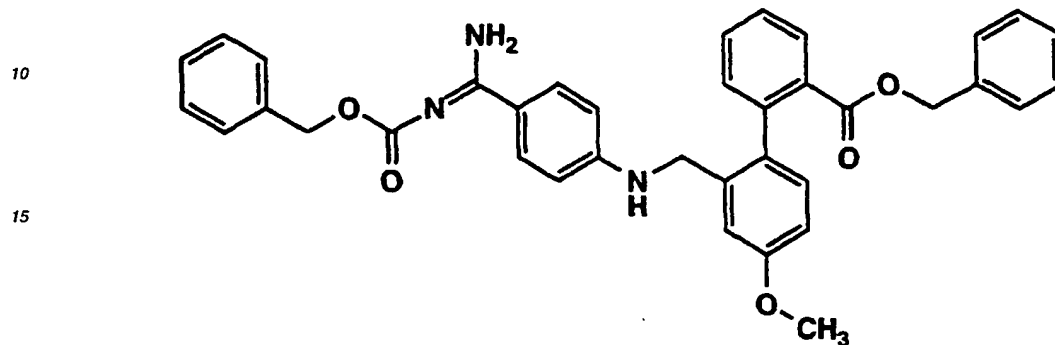
TLC : R_f 0.18 (Toluene : Ethyl acetate = 6 : 1) ;

55 NMR (d₆-DMSO) : δ 9.4-8.4 (2H, br), 8.0-6.8 (23H, m), 6.46 (2H, d, J = 8.8 Hz), 5.12 (1H, d, J = 12.8 Hz), 5.05 (2H, s), 5.03 (1H, d, J = 12.8 Hz), 4.11 (2H, d, J = 4.8 Hz).

Example 17(2)

Benzyl 2'-(4-(N²-benzyloxycarbonylamidino)phenylaminomethyl)-4'-methoxy-2-biphenylcarboxylate

5 [0317]



20

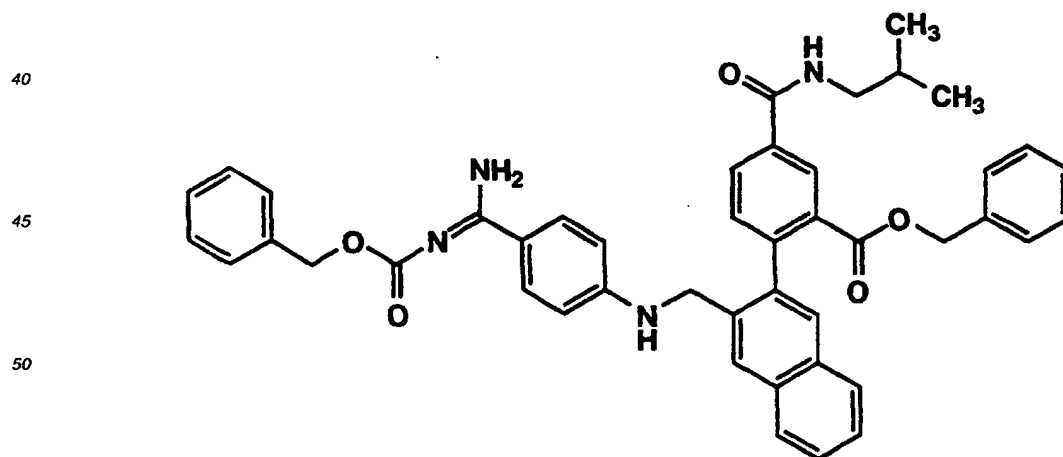
TLC : R_f 0.56 (Chloroform : Ethyl acetate = 8 : 2) ;

25 NMR (CDCl₃) : δ 9.8-9.2 (1H, broad), 7.92 (1H, dd, J = 8.0 Hz, 1.5 Hz), 7.60 (2H, d, J = 9.0 Hz), 7.52-7.10 (13H, m), 7.01 (1H, d, J = 8.0 Hz), 6.90 (1H, d, J = 2.5 Hz), 6.81 (1H, dd, J = 8.0 Hz, 2.5 Hz), 6.27 (2H, d, J = 9.0 Hz), 5.19 (2H, s), 5.13 (1H, d, J = 12 Hz), 5.06 (1H, d, J = 12 Hz), 4.38 (1H, brt, J = 7.0 Hz), 4.00 (2H, d, J = 7.0 Hz), 3.81 (3H, s).

30 Example 17(3)

Benzyl 2-(3-(4-(N²-benzyloxycarbonylamidino)phenylaminomethyl) naphthalen-2-yl)-5-((2-methylpropyl)carbamoyl)benzoate

35 [0318]



50

55

TLC : R_f 0.41 (Hexane : Ethyl acetate = 2 : 3) ;

NMR (CDCl₃) : δ 8.22 (1H, d, J = 2.0 Hz), 7.74-7.90 (4H, m), 7.42-7.58 (8H, m), 7.31-7.36 (3H, m), 7.08-7.23 (3H, m), 6.89-6.92 (2H, m), 6.21-6.25 (3H, m), 5.19 (2H, s), 5.05 (1H, d, J = 12.0 Hz), 5.00 (1H, d, J = 12.0 Hz), 4.31 (1H, br.t, J = 5.2 Hz), 4.19 (2H, br.d, J = 5.2 Hz), 3.28 (2H, t, J = 6.6 Hz), 1.90 (1H, m), 0.97 (6H, d, J = 6.6 Hz).

5 Example 17(4)

Benzyl 2'-(4-(N²-benzyloxycarbonylamidino)phenylaminomethyl)-4'-methoxy-4-((2-methylpropyl)carbamoyl)-2-biphenylcarboxylate

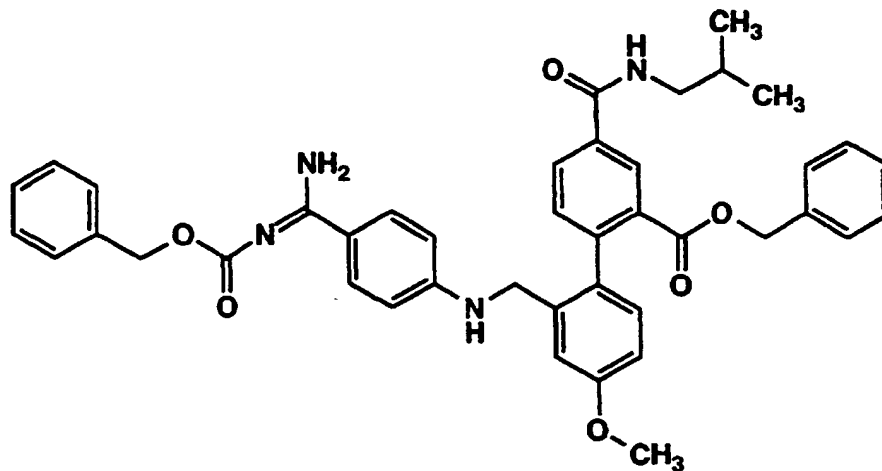
10 [0319]

15

20

25

30



35 TLC : R_f 0.37(Hexane : Ethyl acetate = 2 : 3) ;

NMR (CDCl₃) : δ 8.21 (1H, d, J = 2.0 Hz), 7.84 (1H, dd, J = 2.0, 8.0 Hz), 7.52 (2H, d, J = 8.8 Hz), 7.41-7.46 (2H, m), 7.24-7.36 (7H, m), 7.10-7.15 (2H, m), 6.97 (1H, d, J = 8.4 Hz), 6.88 (1H, d, J = 2.6 Hz), 6.80 (1H, dd, J = 2.6, 8.4 Hz), 6.39 (1H, br.t, J = 6.6 Hz), 6.18 (2H, d, J = 8.8 Hz), 5.18 (2H, s), 5.12 (1H, d, J = 12.0 Hz), 5.06 (1H, d, J = 12.0 Hz), 4.27 (1H, br.t, J = 5.0 Hz), 3.98 (2H, br.t, J = 5.0 Hz), 3.81 (3H, s), 3.24 (2H, t, J = 6.6 Hz), 1.87 (1H, m), 0.94 (6H, d, J = 6.6 Hz).

40

45

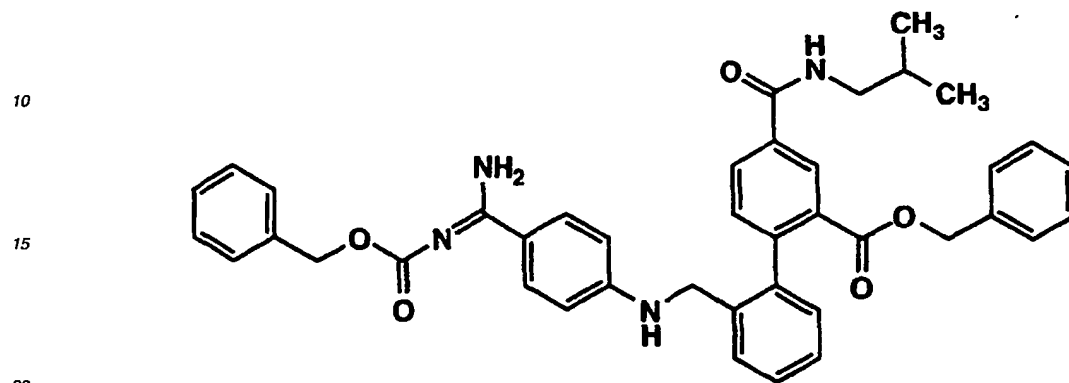
50

55

Example 17(5)

Benzyl 2'-[4-(N²-benzyloxycarbonylamidino)phenylaminomethyl]-4-[(2-methylpropyl)carbamoyl]-2-biphenylcarboxylate

5 [0320]



20

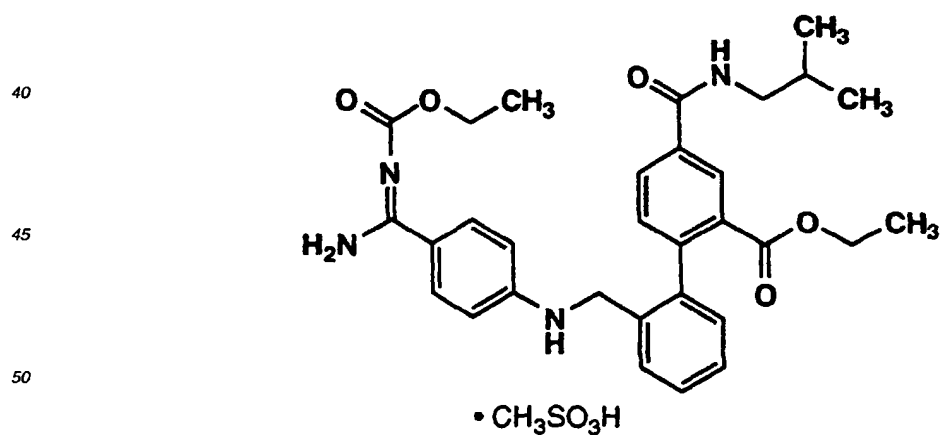
TLC : R_f 0.70 (Chloroform : Ethyl acetate = 1 : 1) ;

25 NMR (d₆-DMSO) : δ 9.3-8.6 (2H, broad), 8.69 (1H, brt, J = 5.5 Hz), 8.37 (1H, d, J = 2.0 Hz), 8.08 (1H, dd, J = 8.0 Hz, 2.0 Hz), 7.71 (2H, d, J = 9.0 Hz), 7.48 (1H, d, J = 8.0 Hz), 7.40-7.20 (11H, m), 7.18-7.09 (2H, m), 7.05 (1H, d, J = 7.5 Hz), 6.76 (1H, brt, J = 5.5 Hz), 6.40 (2H, d, J = 9.0 Hz), 5.11 (2H, s), 5.05 (2H, s), 3.97 (2H, d, J = 5.5 Hz), 3.10 (2H, t, J = 6.0 Hz), 1.85 (1H, m), 0.88 (6H, d, J = 6.5 Hz).

30 Example 17(6)

Ethyl 2'-[4-(N²-ethoxycarbonylamidino)phenylaminomethyl]-4-[(2-methyl propyl)carbamoyl]-2-biphenylcarboxylate methanesulfonate

35 [0321]



50

55

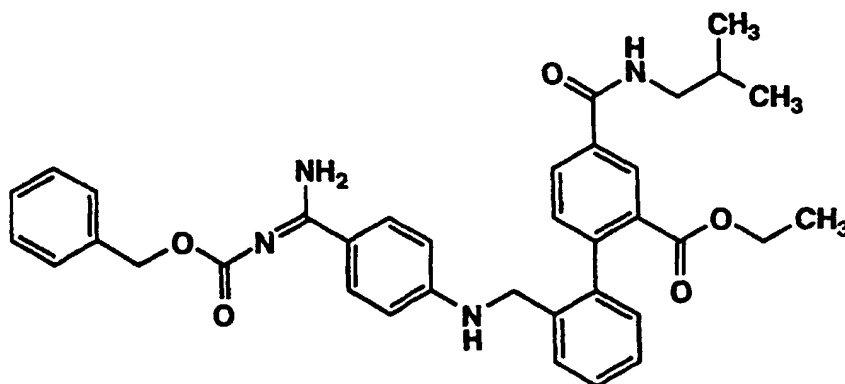
TLC : R_f 0.42 (Chloroform : Ethyl acetate = 1 : 1) ;NMR (d₆-DMSO) : δ 11.80 (1H, brs), 10.61 (1H, brs), 9.99 (1H, brs), 8.70 (1H, brt, J = 6.0 Hz), 8.34 (1H, d, J = 2.0

Hz), 8.07 (1H, dd, J = 8.0 Hz, 2.0 Hz), 7.60-7.46 (1H, broad), 7.57 (2H, d, J = 8.5 Hz), 7.50 (1H, d, J = 8.0 Hz), 7.38-7.26 (3H, m), 7.07 (1H, d, J = 7.5 Hz), 6.53 (2H, d, J = 8.5 Hz), 4.30 (2H, q, J = 7.0 Hz), 4.20-3.96 (4H, m), 3.11 (2H, t, J = 6.5 Hz), 2.30 (3H, s), 1.93-1.79 (1H, m), 1.30 (3H, t, J = 7.0 Hz), 0.90 (3H, t, J = 7.0 Hz), 0.90 (6H, d, J = 7.0 Hz).

Example 17(7)

Ethyl 2'-(4-(N²-benzyloxycarbonylamidino)phenylaminomethyl)-4-((2-methylpropyl)carbamoyl)-2-biphenylcarboxylate

[0322]



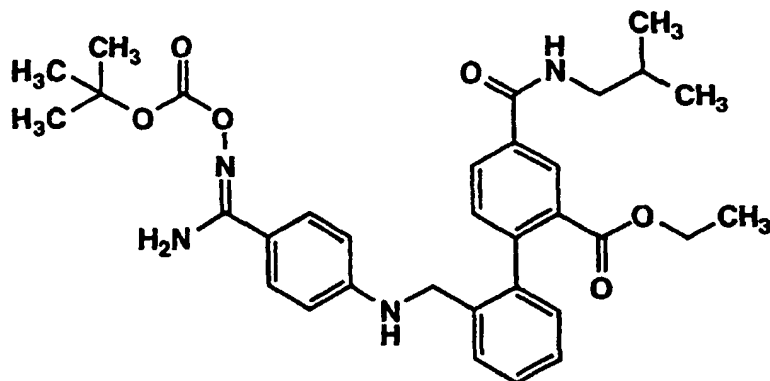
TLC : R_f 0.59 (Chloroform : Ethyl acetate = 1 : 1) ;

NMR (d₆-DMSO) : δ 9.4-8.4 (2H, broad), 8.69 (1H, brt, J = 6.0 Hz), 8.33 (1H, d, J = 2.0 Hz), 8.07 (1H, dd, J = 8.0 Hz, 2.0 Hz), 7.73 (2H, d, J = 9.0 Hz), 7.50 (1H, d, J = 8.0 Hz), 7.40-7.24 (8H, m), 7.04 (1H, d, J = 7.0 Hz), 6.87 (1H, brt, J = 6.0 Hz), 6.43 (2H, d, J = 9.0 Hz), 5.05 (2H, s), 4.10-3.93 (2H, m), 4.02 (2H, q, J = 7.0 Hz), 3.10 (2H, t, J = 6.5 Hz), 1.92-1.78 (1H, m), 0.89 (6H, d, J = 6.5 Hz), 0.89 (3H, t, J = 7.0 Hz).

Example 17(8)

Ethyl 2'-(4-(N²-t-butoxycarbonyloxyamidino)phenylaminomethyl)-4-((2-methylpropyl)carbamoyl)-2-biphenylcarboxylate

[0323]



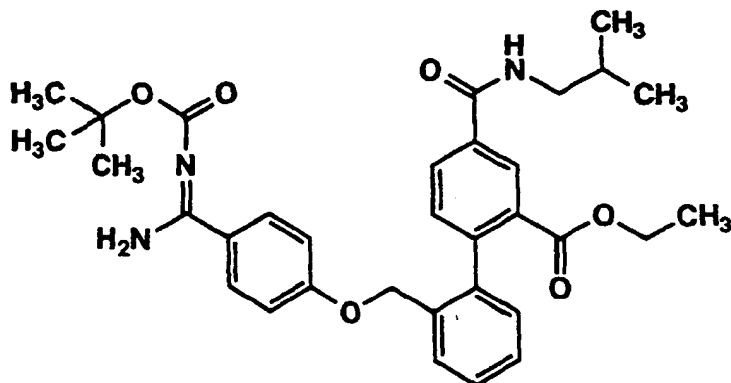
TLC : Rf 0.68 (Chloroform : Ethyl acetate = 1 : 1) ;

NMR (d_6 -DMSO) : δ 8.69 (1H, brt, J = 6.0 Hz), 8.33 (1H, d, J = 2.0 Hz), 8.07 (1H, dd, J = 8.0 Hz, 2.0 Hz), 7.50 (1H, d, J = 8.0 Hz), 7.39-7.23 (5H, m), 7.04 (1H, dd, J = 7.5 Hz, 1.5 Hz), 6.53 (1H, brt, J = 6.0 Hz), 6.41 (2H, d, J = 9.0 Hz), 6.34 (2H, brs), 4.10-3.85 (4H, m), 3.11 (2H, t, J = 6.5 Hz), 1.92-1.79 (1H, m), 1.44 (9H, s), 0.89 (3H, t, J = 7.0 Hz), 0.89 (6H, d, J = 6.5 Hz).

Example 17(9)

Ethyl 2'-[4-(N²-t-butoxycarbonylamidino)phenoxyethyl]-4-[(2-methylpropyl)carbamoyl]-2-biphenylcarboxylate

[0324]



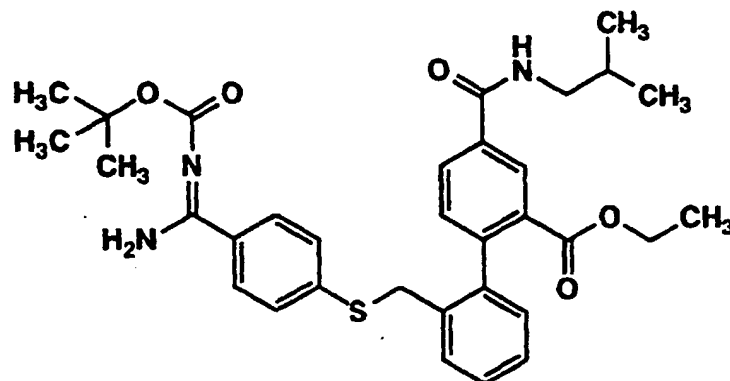
TLC : Rf 0.36 (Hexane : Ethyl acetate = 1 : 1) ;

NMR ($CDCl_3$) : δ 9.8-8.8 (1H, broad), 8.28 (1H, d, J = 2.0 Hz), 7.91 (1H, dd, J = 8.0 Hz, 2.0 Hz), 7.71 (2H, d, J = 9.0 Hz), 7.53 (1H, dd, J = 7.5 Hz, 1.5 Hz), 7.41 (1H, td, J = 7.5 Hz, 1.5 Hz), 7.37 (1H, d, J = 8.0 Hz), 7.36 (1H, td, J = 7.5 Hz, 1.5 Hz), 7.14 (1H, dd, J = 7.5 Hz, 1.5 Hz), 6.77 (2H, d, J = 9.0 Hz), 6.29 (1H, brt, J = 6.5 Hz), 4.81 (2H, s), 4.06 (2H, q, J = 7.0 Hz), 3.31 (2H, t, J = 6.5 Hz), 1.99-1.87 (1H, m), 1.54 (9H, s), 0.99 (6H, d, J = 7.0 Hz), 0.96 (3H, t, J = 7.0 Hz).

Example 17(10)

Ethyl 2'-[4-(N²-t-butoxycarbonylamidino)phenylthiomethyl]-4-[(2-methylpropyl)carbamoyl]-2-biphenylcarboxylate

[0325]



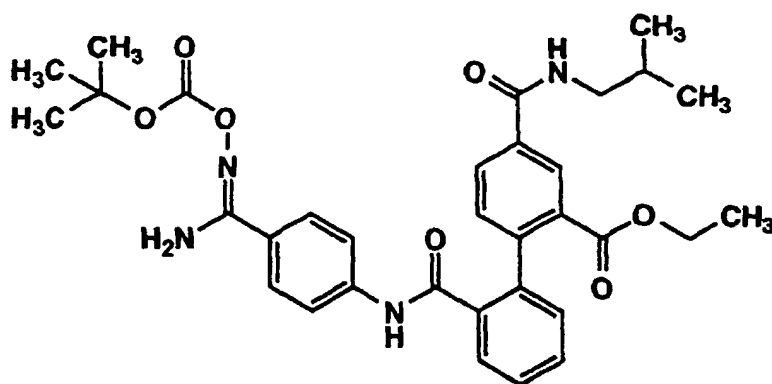
TLC : Rf 0.40 (Hexane : Ethyl acetate = 1 : 1) ;

NMR (CDCl₃) : δ 8.26 (1H, d, J = 1.8 Hz), 7.81 (1H, dd, J = 1.8, 8.0 Hz), 7.56 (2H, d, J = 9.0 Hz), 7.42 (1H, dd, J = 1.8, 8.0 Hz), 7.32 (1H, dt, J = 1.8, 8.0 Hz), 7.27 (1H, dt, J = 1.8, 8.0 Hz), 7.23 (1H, d, J = 8.0 Hz), 7.06 (1H, dd, J = 1.8, 8.0 Hz), 7.02 (2H, d, J = 9.0 Hz), 6.46 (1H, br.s), 4.06 (2H, q, J = 7.4 Hz), 3.94 (1H, d, J = 13.2 Hz), 3.86 (1H, d, J = 13.2 Hz), 3.29 (2H, t, J = 6.6 Hz), 1.91 (1H, m), 1.53 (9H, s), 0.97 (6H, d, J = 6.6 Hz), 0.96 (3H, t, J = 7.4 Hz).

Example 18

Ethyl 2'-[4-(N²-t-butoxycarbonyloxyamidino)phenylcarbamoyl]-4-[(2-methylpropyl)carbamoyl]-2-biphenylcarboxylate

[0326]



[0327] 4'-[(2-methylpropyl)carbamoyl]-2'-ethoxycarbonyl-2-biphenyl carboxylic acid (1.0 g) which was prepared by the same procedure as a series of reaction of Reference Example 4 → Reference Example 5, using ethyl 2-trifluoromethylsulfonyloxy-5-[(2-methylpropyl)carbamoyl]benzoate, was dissolved into ethyl acetate (20 ml). Thionyl chloride (0.22 ml) was dropped into the above solution. The mixture was stirred for 15 minutes at 50 °C. The reaction mixture was cooled to room temperature, and concentrated. A solution of the prepared acyl chloride compound in methylene chloride (10 ml) and triethylamine (0.57 ml) were added to a solution of 4-(N²-t-butoxycarbonyloxyamidino)aniline in

methylene chloride (10 ml) at 0 °C. The mixture was stirred for 1 hour at room temperature. The reaction mixture was diluted with ethyl acetate (150 ml), and washed with a saturated aqueous solution of sodium chloride (75 ml, 2 times). The organic layer was dried over anhydrous magnesium sulfate and concentrated. The residue was purified by column chromatography on silica gel (methylene chloride : methanol = 100 : 1) to give the present compound (1.56 g) having the following physical data.

TLC : Rf 0.62 (Chloroform : Methanol = 10 : 1) .

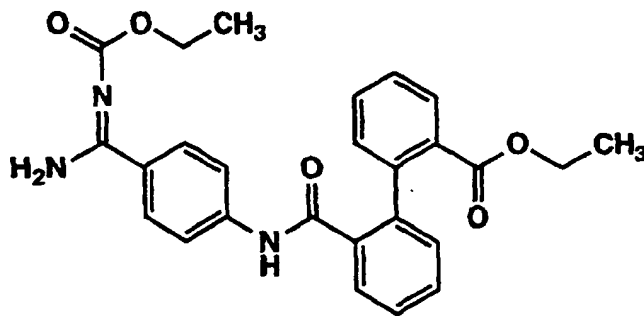
Example 18(1) — Example 18(10)

[0328] The following compounds were obtained by the same procedure as a series of reaction of Example 18, using a corresponding derivative instead of the starting compound in Example 18.

Example 18(1)

Ethyl 2'-4-(N²-ethoxycarbonylamidino)phenylcarbamoyl)-2-biphenylcarboxylate

[0329]



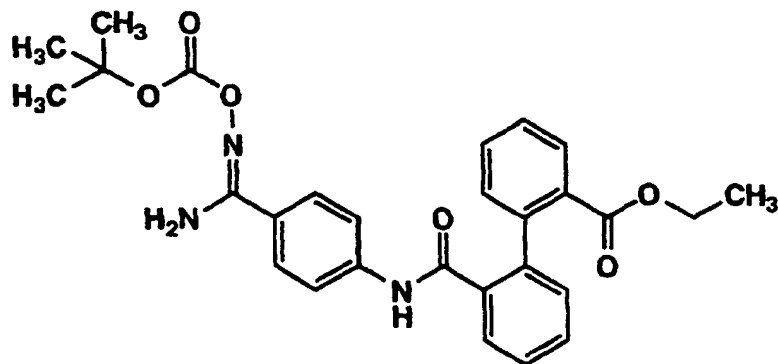
TLC : Rf 0.66 (Chloroform : Methanol : Water = 9 : 1 : 0.1) ;

NMR (d₆-DMSO) : δ 10.27 (1H, s), 9.3-8.7 (2H, broad), 7.89 (2H, d, J = 9.0 Hz), 7.77 (1H, dd, J = 7.5 Hz, 1.5 Hz), 7.70-7.48 (6H, m), 7.42 (1H, td, J = 7.5 Hz, 1.5 Hz), 7.34-7.24 (2H, m), 4.04 (2H, q, J = 7.0 Hz), 3.96 (2H, q, J = 7.0 Hz), 1.20 (3H, t, J = 7.0 Hz), 0.88 (3H, t, J = 7.0 Hz).

Example 18(2)

Ethyl 2'-(4-(N²-t-butoxycarbonyloxyamidino)phenylcarbamoyl)-2-biphenylcarboxylate

[0330]



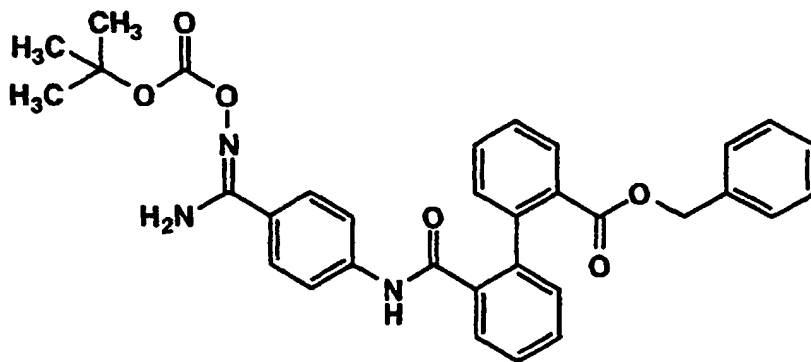
TLC : Rf 0.46 (Chloroform : Ethyl acetate = 1 : 1) ;

NMR (CDCl₃) : δ 8.67 (1H, brs), 7.82-7.76 (2H, m), 7.53-7.35 (6H, m), 7.27-7.22 (3H, m), 7.13-7.09 (1H, m), 5.01 (2H, brs), 4.30-4.22 (2H, m), 1.54 (9H, s), 1.20 (3H, t, J = 7.0 Hz).

Example 18(3)

Benzyl 2'-(4-(N²-t-butoxycarbonyloxyamidino)phenylcarbamoyl)-2-biphenylcarboxylate

[0331]



TLC : Rf 0.77 (Hexane : Ethyl acetate = 1 : 2) ;

NMR (CDCl₃) : δ 8.40 (1H, brs), 7.82 (1H, dd, J = 1.0, 8.0 Hz), 7.72 (1H, dd, J = 1.0, 8.0 Hz), 7.51 - 7.30 (8H, m), 7.25 - 7.17 (2H, m), 7.10 (2H, brd, J = 8.5 Hz), 5.22 (2H, d, J = 12 Hz), 4.95 (2H, brs), 1.57 (9H, s).

Example 18(4)

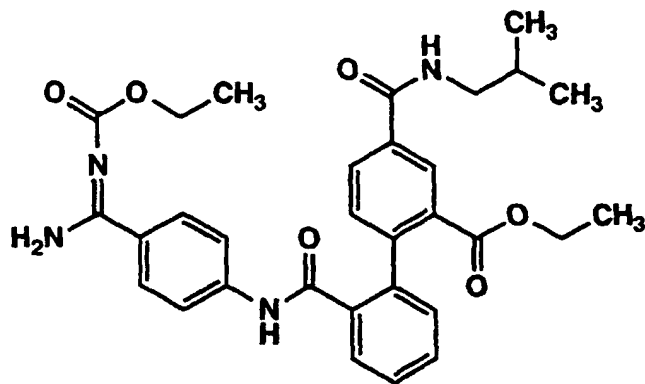
Ethyl 2'-(4-(N²-ethoxycarbonylamidino)phenylcarbamoyl)-4-((2-methylpropyl)carbamoyl)-2-biphenylcarboxylate

5 [0332]

10

15

20



25

TLC : Rf 0.62 (Chloroform : Methanol = 10 : 1) ;

NMR (d₆-DMSO) : δ 10.39 (1H, s), 9.2-8.8 (2H, br), 8.65 (1H, t, J = 7.0 Hz), 8.23 (1H, d, J = 2.0 Hz), 8.01 (1H, dd, J = 2.0, 8.0 Hz), 7.89 (2H, d, J = 8.8 Hz), 7.8-7.4 (5H, m), 7.39 (1H, d, J = 8.0 Hz), 7.29 (1H, dd, J = 2.0, 7.0 Hz), 4.05 (2H, q, J = 7.2 Hz), 3.99 (2H, q, J = 7.2 Hz), 3.08 (2H, t, J = 7.0 Hz), 1.84 (1H, like septet, J = 7.0 Hz), 1.20 (3H, t, J = 7.2 Hz), 0.89 (3H, t, J = 7.2 Hz), 0.88 (6H, d, J = 7.0 Hz).

30

Example 18(5)

Ethyl 2'-(4-(N²-ethoxycarbonylamidino)phenylcarbamoyl)-4-((2-methylpropyl)carbamoyl)-2-biphenylcarboxylate methanesulfonate

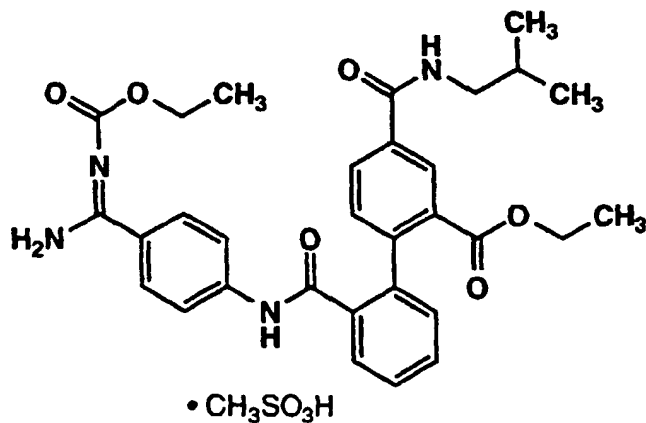
35

[0333]

40

45

50



55

TLC : Rf 0.62 (Chloroform : Methanol = 10 : 1) ;

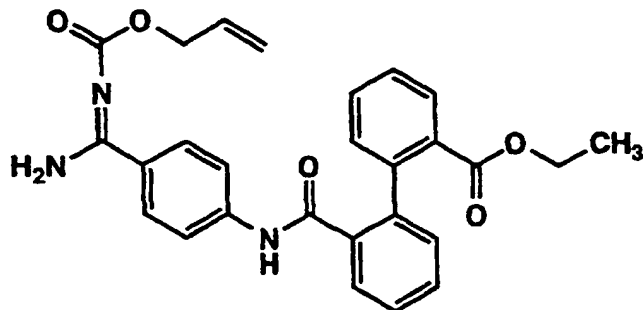
NMR (d₆-DMSO) : δ 12.32 (1H, br), 11.12 (1H, br.s), 10.63 (1H, s), 10.43 (1H, br.s), 8.68 (1H, br.t, J = 6.4 Hz), 8.23

(1H, d, J = 1.6 Hz), 8.03 (1H, dd, J = 1.6, 7.9 Hz), 7.74 (4H, like s), 7.8-7.6 (1H, m), 7.7-7.5 (2H, m), 7.41 (1H, d, J = 7.8 Hz), 7.31 (1H, dd, J = 1.6, 7.8 Hz), 4.33 (2H, q, J = 6.8 Hz), 3.98 (2H, q, J = 6.8 Hz), 3.09 (2H, t, J = 6.4 Hz), 2.37 (3H, s), 1.84 (1H, like septet, J = 6.4 Hz), 1.31 (3H, t, J = 6.8 Hz), 0.89 (3H, t, J = 6.8 Hz), 0.88 (6H, d, J = 6.4 Hz).

Example 18(6)

Ethyl 2'-(4-(N²-(2-propenyloxycarbonyl)amidino)phenylcarbamoyl)-2-biphenylcarboxylate

[0334]



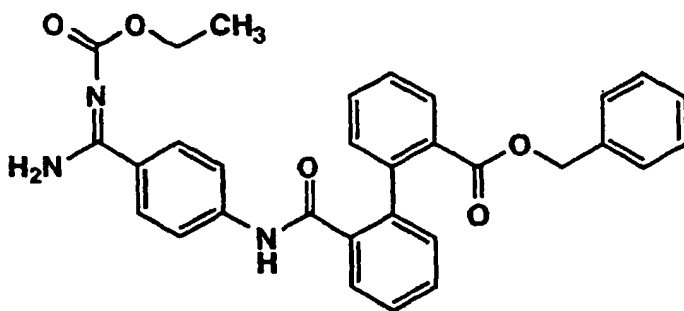
TLC : Rf 0.69 (Chloroform : Methanol : Water = 9 : 1 : 0.1) ;

NMR (CDCl₃) : δ 8.95 (1H, s), 7.80 (2H, d, J = 9.0 Hz), 7.76 (1H, m), 7.34-7.51 (4H, m), 7.33 (2H, d, J = 9.0 Hz), 7.23 (1H, m), 7.12 (1H, m), 5.97 (1H, m), 5.22-5.42 (2H, m), 4.61-4.68 (2H, m), 4.28 (2H, q, J = 7.2 Hz), 1.23 (3H, t, J = 7.2 Hz).

Example 18(7)

Benzyl 2'-(4-(N²-ethoxycarbonylamidino)phenylcarbamoyl)-2-biphenylcarboxylate

[0335]



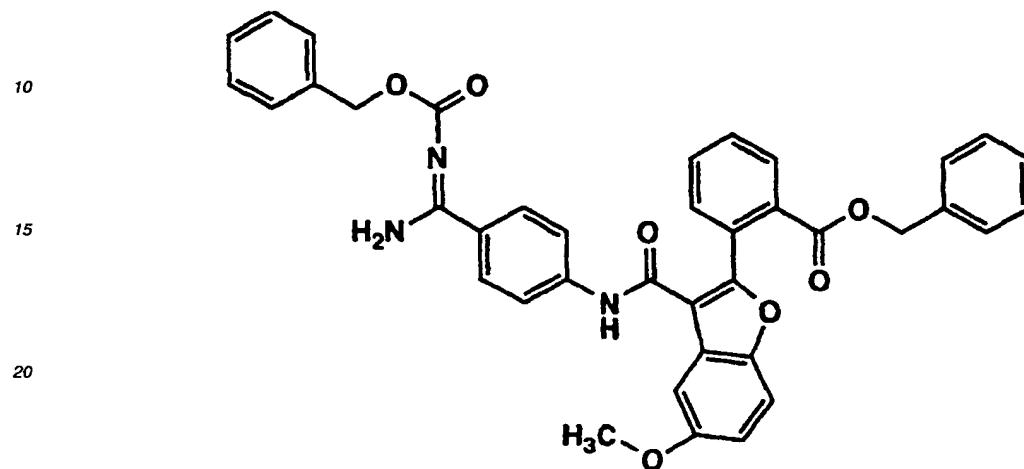
TLC : Rf 0.75 (Chloroform : Methanol = 10 : 1) ;

NMR (CDCl₃) : δ 10.0-9.0 (1H, br), 8.5 (1H, s), 7.83 (1H, dd, J = 1.6, 7.4 Hz), 7.8-7.6 (3H, m), 7.6-7.3 (6H, m), 7.3-7.0 (7H, m), 7.0-6.2 (1H, br), 5.24 (1H, d, J = 14.6 Hz), 5.18 (1H, d, J = 14.6 Hz), 4.19 (2H, q, J = 7.4 Hz), 1.33 (3H, t, J = 7.4 Hz).

Example 18(8)

Benzyl 2-(3-(4-(N²-benzyloxycarbonylamidino)phenylcarbamoyl)-5-methoxybenzofuran-2-yl)benzoate

5 [0336]



25

TLC : R_f 0.45 (Hexane : Ethyl acetate = 1 : 1) ;
 30 NMR (d₆-DMSO) : δ 10.30 (1H, s); 9.3-8.9 (2H, broad), 7.96 (2H, d, J = 9.0 Hz), 7.91 (1H, dd, J = 7.5 Hz, 2.0 Hz), 7.76-7.70 (4H, m), 7.64 (1H, td, J = 7.5 Hz, 2.0 Hz), 7.53 (1H, d, J = 9.0 Hz), 7.41-7.29 (5H, m), 7.25 (1H, d, J = 2.0 Hz), 7.24-7.18 (3H, m), 7.16-7.13 (2H, m), 7.02 (1H, dd, J = 9.0 Hz, 2.0 Hz), 5.10 (4H, s), 3.83 (3H, s).

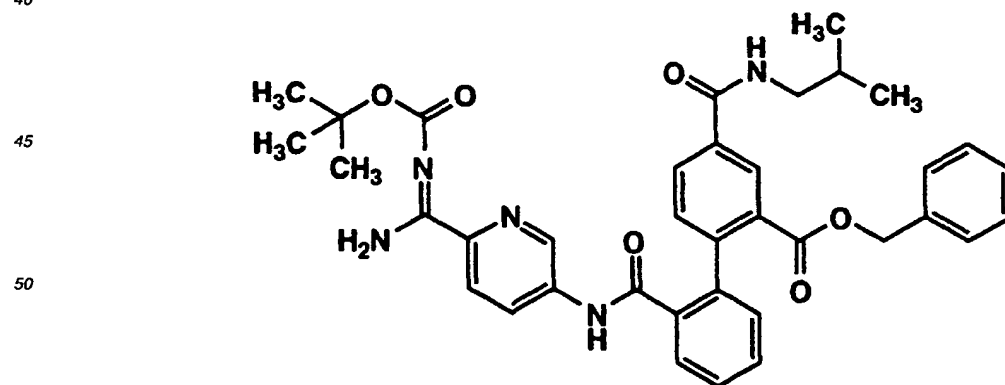
Example 18(9)

35

Benzyl 2'-(6-(N²-t-butoxycarbonylamidino)pyridin-3-ylcarbamoyl)-4-((2-methylpropyl)carbamoyl)-2-biphenylcarboxylate

[0337]

40



55

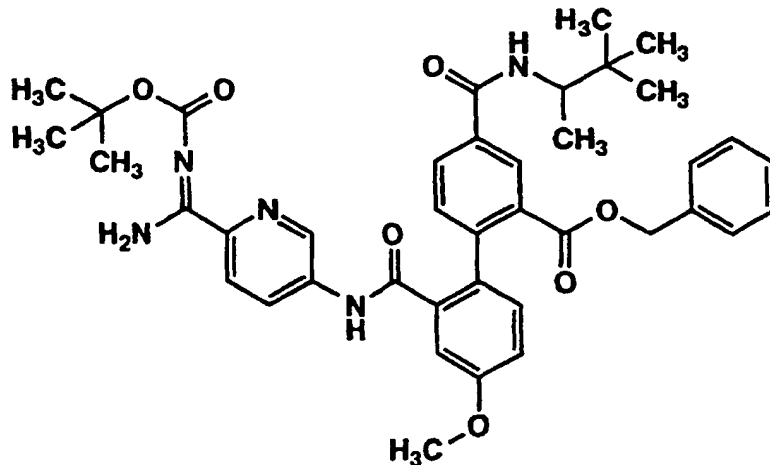
TLC : Rf 0.49 (Chloroform : Methanol = 10 : 1) ;

NMR (CDCl₃) : δ 9.25 (1H, br s), 8.69 (1H, s), 8.28 (1H, d, J = 1.6 Hz), 8.23 (1H, d, 6.2 Hz), 8.21 (1H, s), 8.10 (1H, br s), 7.81 (1H, dd, J = 1.6, 7.6 Hz), 7.70-7.71 (2H, m), 7.58-7.42 (2H, m), 7.40-7.20 (6H, m), 7.09-7.04 (2H, m), 6.25 (1H, t, J = 5.8 Hz), 5.29 (1H, d, J = 11.6 Hz), 5.17 (1H, d, J = 11.6 Hz), 3.26 (2H, t, J = 6.2 Hz), 1.88 (1H, septet, J = 6.2 Hz), 1.54 (9H, s), 0.96 (6H, d, J = 6.2 Hz).

Example 18(10)

Benzyl 2'-(6-(N²-t-butoxycarbonylamidino)pyridin-3-ylcarbamoyl)-4'-methoxy-4-((1, 2, 2-trimethylpropyl)carbamoyl)-2-biphenylcarboxylate

[0338]



TLC : Rf 0.45 (Chloroform : Methanol : Water = 9 : 1 : 0.1) ;

NMR (CDCl₃) : δ 9.3-9.2 (1H, broad), 8.77 and 8.73 (1H, s), 8.28-8.20 (2H, m), 8.20-8.08 (1H, broad), 7.81-7.70 (2H, m), 7.38-7.20 (7H, m), 6.99-6.92 (2H, m), 5.91 (1H, d, J = 9.5 Hz), 5.31-5.09 (2H, m), 4.08 (1H, dq, J = 9.5 Hz, 7.0 Hz), 3.90 (3H, s), 1.55 (9H, s), 1.14 (3H, d, J = 7.0 Hz), 0.95 (9H, s).

Example 19 - Example 19(182)

[0339] The following compounds were obtained by the same procedure as a series of reaction of Example 4, Example 2, Example 11 or Reference Example 8, using the compound prepared in Example 7 - Example 7(83), Example 7(86) - Example 7(98), Example 8 - Example 8(6), Example 9 - Example 9(31), Example 12 - Example 12(3), Example 13, Example 14 - Example 14(2), Example 15 - Example 15(1), Example 16, Example 17 - Example 17(5), Example 17(7) - Example 17(8), Example 18, Example 18(2) - Example 18(3), Example 18(7), Example 7(99) - Example 7(113), Example 8(7), Example 17(9), Example 18(8) - Example 18(9), Example 7(114) - Example 7(115), Example 17(10) and Example 18(10).

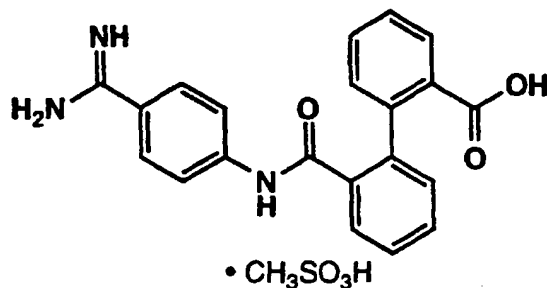
Example 19

2'-(4-amidinophenylcarbamoyl)-2-biphenylcarboxylic acid methanesulfonate

5 [0340]

10

15



20

TLC : R_f 0.16 (Chloroform : Methanol : Water = 8 : 2 : 0.2) ;NMR (d₆-DMSO) : δ 10.39 (1H, s), 9.14 (2H, s), 8.79 (2H, s), 7.82 (1H, dd, J = 1.4, 7.6 Hz), 7.73 (2H, d, J = 9.0 Hz), 7.64-7.69 (3H, m), 7.48-7.56 (3H, m), 7.40 (1H, dt, J = 1.4, 7.6 Hz), 7.23-7.28 (2H, m), 2.35 (3H, s).

25

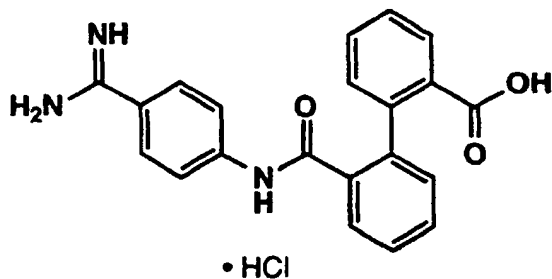
Example 19(1)

2'-(4-amidinophenylcarbamoyl)-2-biphenylcarboxylic acid hydrochloride

30 [0341]

35

40



45

TLC : R_f 0.12 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;NMR (d₆-DMSO) : δ 13.2-12.2 (1H, broad), 10.46 (1H, s), 9.32 (2H, s), 9.16 (2H, s), 7.84-7.77 (3H, m), 7.72-7.64 (3H, m), 7.60-7.37 (4H, m), 7.28-7.20 (2H, m).

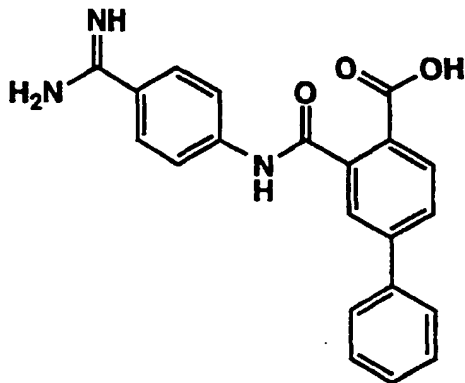
50

55

Example 19(2)

3-(4-amidinophenylcarbamoyl)-4-biphenylcarboxylic acid

5 [0342]



25

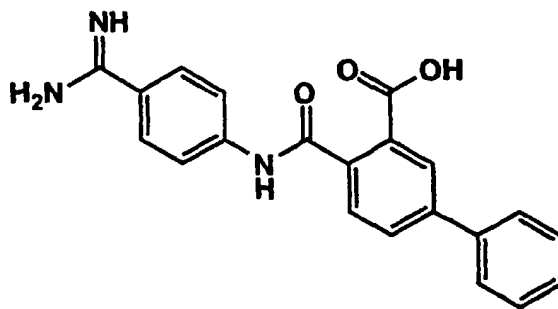
TLC : Rf 0.31 (Ethyl acetate : Acetic acid : Water = 6 : 1 : 1) ;

NMR (d_6 -DMSO + 1 drop of $MeSO_3H$) : δ 10.90 (1H, s), 9.20 (2H, s), 9.02 (2H, s), 8.04-7.64 (9H, m), 7.60-7.38 (3H, m).

30 Example 19(3)

4-(4-amidinophenylcarbamoyl)-3-biphenylcarboxylic acid

35 [0343]



40

45

50

TLC : Rf 0.35 (Ethyl acetate : Acetic acid : Water = 6 : 1 : 1) ;

NMR (d_6 -DMSO + 1 drop of $MeSO_3H$) : δ 11.59 (1H, s), 10.05 (2H, s), 9.05 (2H, s), 8.10 (1H, d, $J = 2$ Hz), 8.00-7.62 (8H, m), 7.58-7.38 (3H, m).

55

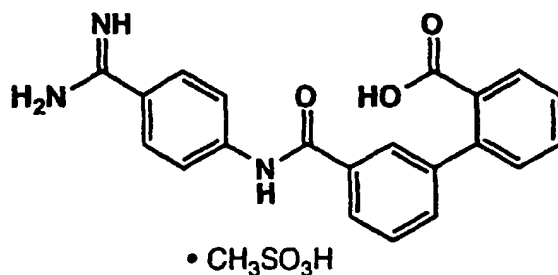
Example 19(4)

3'-(4-amidinophenylcarbamoyl)-2-biphenylcarboxylic acid methanesulfonate

5 [0344]

10

15



20

TLC : R_f 0.25 (Ethyl acetate : Acetic acid : Water = 6 : 1 : 0.5) ;NMR (d₆-DMSO) : δ 13.0-12.7 (1H, broad), 10.71 (1H, s), 9.23 (2H, s), 8.96 (2H, s), 8.06-7.96 (4H, m), 7.90-7.78 (3H, m), 7.68-7.43 (5H, m), 2.36 (3H, s).

25

Example 19(5)

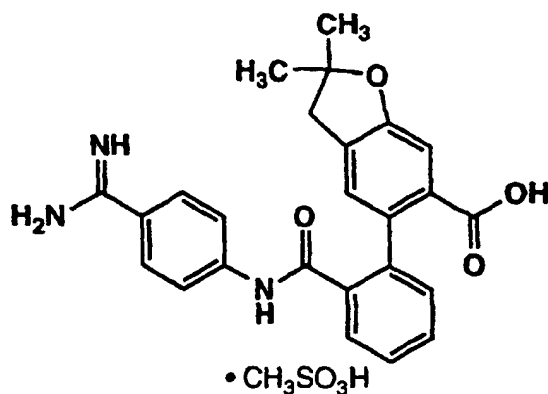
2, 3-dihydro-2, 2-dimethyl-5-(2-(4-amidinophenylcarbamoyl) phenyl)-6-benzofurancarboxylic acid methanesulfonate

30 [0345]

35

40

45



50

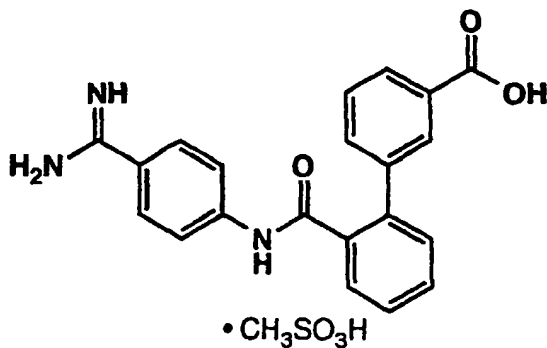
TLC : R_f 0.40 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;NMR (d₆-DMSO) : δ 13.0-12.3 (1H, broad), 10.28 (1H, s), 9.16 (2H, s), 8.90 (2H, s), 7.75 (2H, d, J = 9 Hz), 7.66 (2H, d, J = 9 Hz), 7.62 (1H, dd, J = 7 Hz, 2 Hz), 7.57-7.41 (2H, m), 7.22 (1H, dd, J = 7 Hz, 2 Hz), 7.05 (1H, s), 7.04 (1H, s), 3.00 (2H, s), 2.36 (3H, s), 1.40 (6H, s).

55

Example 19(6)

2'-(4-amidinophenylcarbamoyl)-3-biphenylcarboxylic acid methanesulfonate

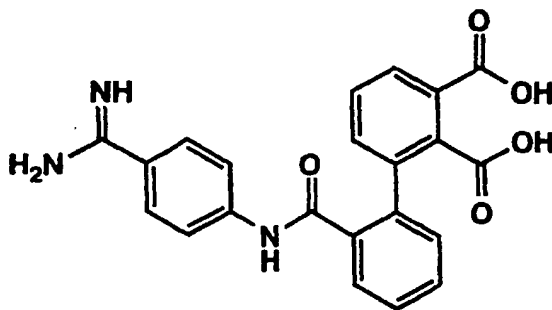
[0346]

TLC : R_f 0.34 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;NMR (d₆-DMSO) : δ 13.3-12.7 (1H, broad), 10.71 (1H, s), 9.19 (2H, s), 8.98 (2H, s), 8.03 (1H, s), 7.88 (1H, d, J = 8 Hz), 7.80-7.43 (10H, m), 2.38 (3H, s).

Example 19(7)

2'-(4-amidinophenylcarbamoyl)-2, 3-biphenyldicarboxylic acid

[0347]

TLC : R_f 0.27 (Chloroform : Methanol : Water = 6 : 4 : 1) ;NMR (d₆-DMSO) : δ 14.0-12.0 (1H, broad), 10.81 (1H, brs), 9.24 (2H, brs), 8.20 (2H, brs), 7.84-7.24 (11H, m).

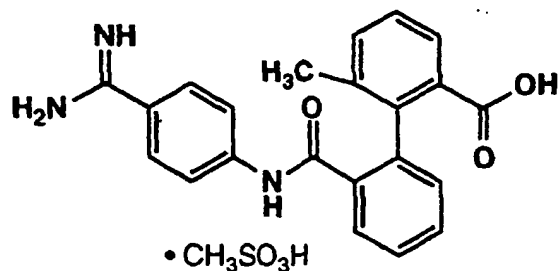
Example 19(8)

2'-(4-amidinophenylcarbamoyl)-6-methyl-2-biphenylcarboxylic acid methanesulfonate

5 [0348]

10

15



20

TLC : R_f 0.12 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;NMR (d₆-DMSO) : δ 13.2-12.2 (1H, broad), 10.42 (1H, s), 9.15 (2H, brs), 8.91 (2H, brs), 7.75-7.50 (8H, m), 7.39 (1H, d, J = 8 Hz), 7.30 (1H, t, J = 8 Hz), 7.10 (1H, dd, J = 8 Hz, 2 Hz), 2.35 (3H, s), 1.92 (3H, s).

25

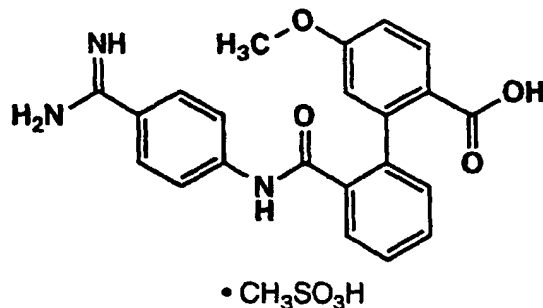
Example 19(9)

2'-(4-amidinophenylcarbamoyl)-5-methoxy-2-biphenylcarboxylic acid methanesulfonate

30 [0349]

35

40



45

TLC : R_f 0.29 (Chloroform : Methanol : Water = 7 : 3 : 0.3) ;NMR (d₆-DMSO) : δ 10.40 (1H, s), 9.15 (2H, s), 8.82 (2H, s), 7.82 (1H, d, J = 8.8 Hz), 7.73 (2H, d, J = 9.0 Hz), 7.68 (2H, d, J = 9.0 Hz), 7.66 (1H, d, J = 8.8 Hz), 7.44-7.58 (2H, m), 7.26 (1H, d, J = 7.8 Hz), 6.92 (1H, dd, J = 2.2, 8.8 Hz), 6.75 (1H, d, J = 2.2 Hz), 3.76 (3H, s), 2.36 (3H, s).

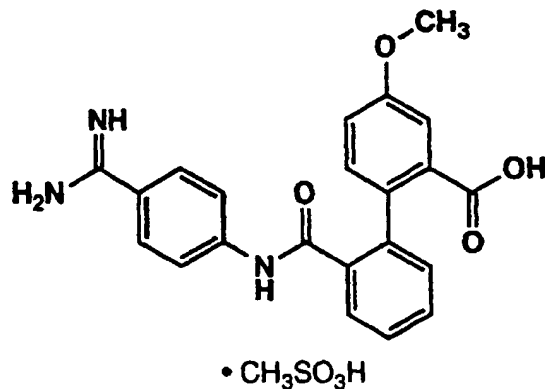
50

55

Example 19(10)

2'-(4-amidinophenylcarbamoyl)-4-methoxy-2-biphenylcarboxylic acid methanesulfonate

5 [0350]

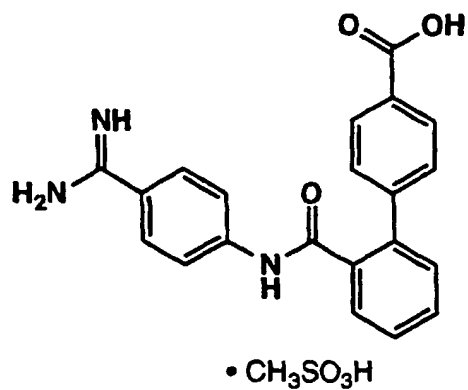


25 TLC : Rf 0.31 (Chloroform : Methanol : Water = 7 : 3 : 0.3) ;
 NMR (d₆-DMSO) : δ 10.38 (1H, s), 9.16 (2H, s), 8.87 (2H, s), 7.75 (2H, d, J = 9.0 Hz), 7.69 (2H, d, J = 9.0 Hz), 7.63 (1H, d, J = 8.0 Hz), 7.53 (1H, t, J = 8.0 Hz), 7.48 (1H, t, J = 8.0 Hz), 7.32 (1H, d, J = 2.2 Hz), 7.23 (1H, d, J = 8.0 Hz), 7.17 (1H, d, J = 8.6 Hz), 7.08 (1H, dd, J = 2.2, 8.6 Hz), 3.79 (3H, s), 2.35 (3H, s).

30 Example 19(11)

2'-(4-amidinophenylcarbamoyl)-4-biphenylcarboxylic acid methanesulfonate

35 [0351]

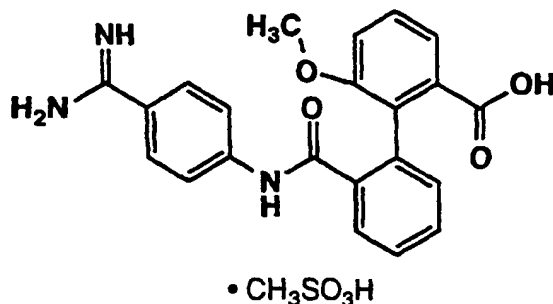


50
 55 TLC : Rf 0.12 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;
 NMR (d₆-DMSO) : δ 12.97 (1H, brs), 10.73 (1H, s), 9.18 (2H, brs), 8.95 (2H, brs), 7.91 (2H, d, J = 8.5 Hz), 7.80-7.50 (10H, m), 2.34 (3H, s).

Example 19(12)

2'-(4-amidinophenylcarbamoyl)-6-methoxy-2-biphenylcarboxylic acid methanesulfonate

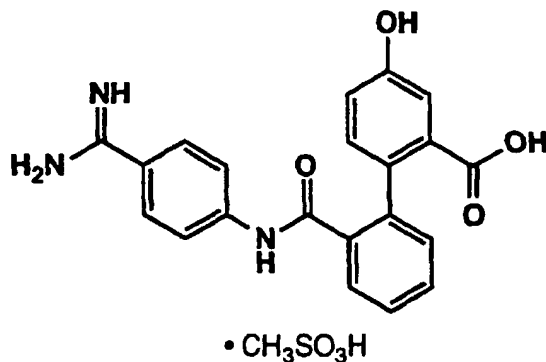
5 [0352]

TLC : R_f 0.30 (Chloroform : Methanol : Water = 7 : 3 : 0.3) ;NMR (d₆-DMSO) : δ 10.34 (1H, s), 9.15 (2H, s), 8.83 (2H, s), 7.73 (4H, s), 7.67 (1H, m), 7.45-7.54 (2H, m), 7.36-7.38 (2H, m), 7.11-7.16 (2H, m), 3.56 (3H, s), 2.34 (3H, s).

Example 19(13)

2'-(4-amidinophenylcarbamoyl)-4-hydroxy-2-biphenylcarboxylic acid methanesulfonate

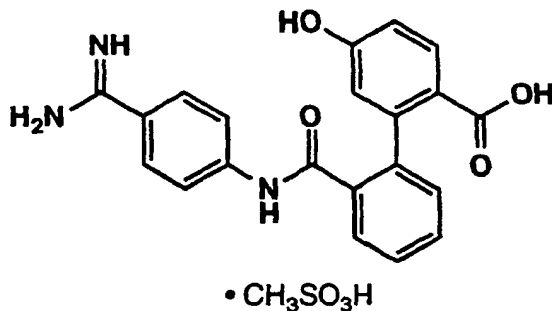
30 [0353]

TLC : R_f 0.19 (Chloroform : Methanol : Water = 7 : 3 : 0.3) ;NMR (d₆-DMSO) : δ 10.25 (1H, s), 9.76 (1H, s), 9.15 (2H, s), 8.82 (2H, s), 7.74 (2H, d, J = 8.8 Hz), 7.66 (2H, d, J = 8.8 Hz), 7.60 (1H, dd, J = 2.0, 7.6 Hz), 7.50 (1H, dt, J = 2.0, 7.6 Hz), 7.45 (1H, dt, J = 2.0, 7.6 Hz), 7.21 (1H, dd, J = 2.0, 7.6 Hz), 7.19 (1H, d, J = 2.4 Hz), 7.03 (1H, d, J = 8.2 Hz), 6.87 (1H, dd, J = 2.4, 8.2 Hz), 2.35 (3H, s).

Example 19(14)

2'-(4-amidinophenylcarbamoyl)-5-hydroxy-2-biphenylcarboxylic acid methanesulfonate

[0354]



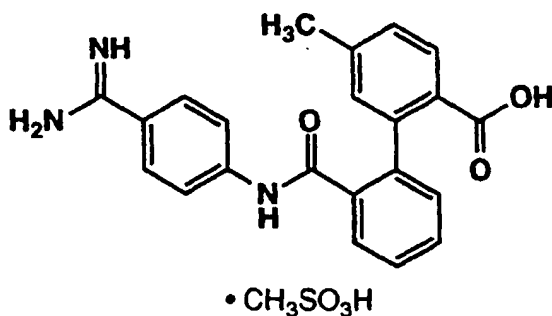
TLC : Rf 0.19 (Chloroform : Methanol : Water = 7 : 3 : 0.3) ;

NMR (d₆-DMSO) : δ 10.34 (1H, s), 10.16 (1H, s), 9.14 (2H, s), 8.78 (2H, s), 7.73 (2H, d, J = 8.8 Hz), 7.72 (1H, d, J = 8.6 Hz), 7.67 (2H, d, J = 8.8 Hz), 7.63 (1H, dd, J = 2.4, 7.2 Hz), 7.47-7.53 (2H, m), 7.20 (1H, dd, J = 2.4, 7.2 Hz), 6.75 (1H, dd, J = 2.4, 8.6 Hz), 6.56 (1H, d, J = 2.4 Hz), 2.34 (3H, s).

Example 19(15)

2'-(4-amidinophenylcarbamoyl)-5-methyl-2-biphenylcarboxylic acid methanesulfonate

[0355]



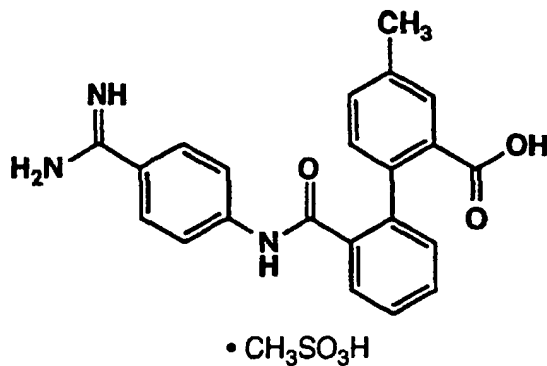
TLC : Rf 0.15 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d₆-DMSO) : δ 10.37 (1H, s), 9.13 (2H, brs), 8.80 (2H, brs), 7.72 (2H, d, J = 8.0 Hz), 7.66 (2H, d, J = 8.0 Hz), 7.70 - 7.60 (2H, m), 7.50 (1H, dt, J = 1.5, 8.0 Hz), 7.45 (1H, dt, J = 1.5, 8.0 Hz), 7.20 (1H, dd, J = 2.0, 7.5 Hz), 7.16 (1H, dd, J = 2.0, 8.0 Hz), 7.01 (1H, s), 5.00 - 3.60 (1H, m), 2.29 (3H, s), 2.27 (3H, s).

Example 19(16)

2'-(4-amidinophenylcarbamoyl)-4-methyl-2-biphenylcarboxylic acid methanesulfonate

5 [0356]



20

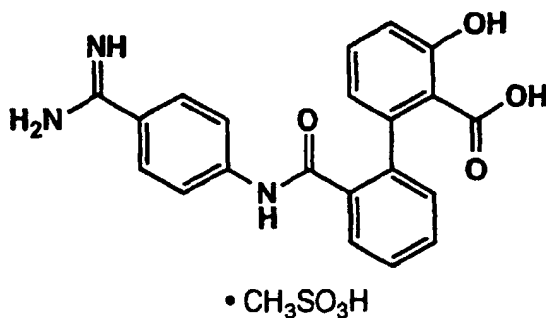
25 TLC : R_f 0.14 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;
 NMR (d₆-DMSO) : δ 10.42 (1H, s), 9.14 (2H, brs), 8.81 (2H, brs), 7.70 (2H, d, J = 8.0 Hz), 7.65 (2H, d, J = 8.0 Hz),
 7.66 - 7.60 (1H, m), 7.61 (1H, s), 7.50 (1H, brt, J = 8.0 Hz), 7.45 (1H, brt, J = 8.0 Hz), 7.30 (1H, d, J = 7.5 Hz), 7.20
 (1H, d, J = 7.5 Hz), 7.10 (1H, d, J = 8.0 Hz), 4.20 - 3.50 (1H, m), 2.31 (6H, s).

Example 19(17)

30

2'-(4-amidinophenylcarbamoyl)-3-hydroxy-2-biphenylcarboxylic acid methanesulfonate

[0357]



45

50

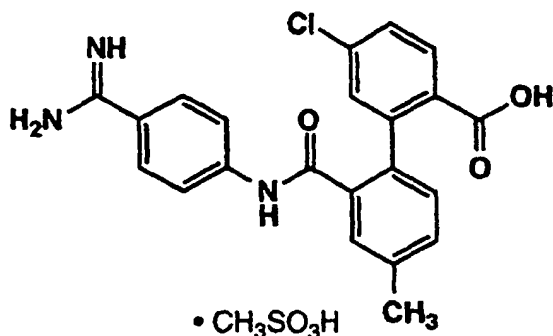
TLC : R_f 0.42 (Chloroform : Methanol : Water = 7 : 3 : 0.3) ;
 NMR (d₆-DMSO) : δ 10.36 (1H, s), 9.16 (2H, s), 8.81 (2H, s), 7.74 (2H, d, J = 8.8 Hz), 7.65 (2H, d, J = 8.8 Hz), 7.50-
 7.65 (3H, m), 7.19-7.30 (2H, m), 6.86 (1H, d, J = 8.4 Hz), 6.61 (1H, d, J = 7.0 Hz), 2.33 (3H, s).

55

Example 19(18)

2'-(4-amidinophenylcarbamoyl)-4'-methyl-5-chloro-2-biphenylcarboxylic acid methanesulfonate

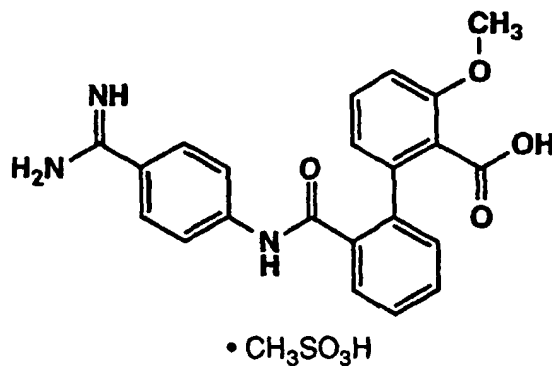
[0358]

TLC : R_f 0.19 (Chloroform : Methanol : Acetic acid = 4 : 1 : 0.1) ;NMR (d₆-DMSO) : δ 13.2-12.0 (1H, br), 10.50 (1H, s), 9.17 (2H, s), 8.85 (2H, s), 7.82 (1H, d, J = 8.4 Hz), 7.74 (4H, s), 7.5-7.3 (3H, m), 7.26 (1H, d, J = 1.8 Hz), 7.18 (1H, d, J = 7.8 Hz), 2.44 (3H, s), 2.35 (3H, s).

Example 19(19)

2'-(4-amidinophenylcarbamoyl)-3-methoxy-2-biphenylcarboxylic acid methanesulfonate

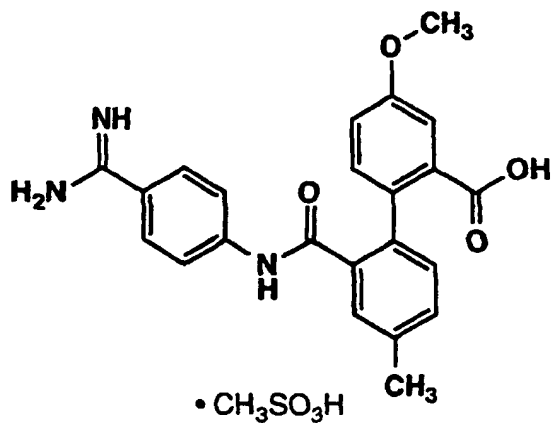
[0359]

TLC : R_f 0.28 (Chloroform : Methanol : Water = 7 : 3 : 0.3) ;NMR (d₆-DMSO) : δ 10.32 (1H, br.s), 9.16 (2H, s), 8.85 (2H, s), 7.75 (2H, d, J = 8.8 Hz), 7.67 (1H, m), 7.64 (2H, d, J = 8.8 Hz), 7.53-7.57 (2H, m), 7.29-7.37 (2H, m), 7.05 (1H, d, J = 8.4 Hz), 6.79 (1H, d, J = 7.6 Hz), 3.83 (3H, s), 2.34 (3H, s).

Example 19(20)

2'-(4-amidinophenylcarbamoyl)-4'-methyl-4-methoxy-2-biphenylcarboxylic acid methanesulfonate

5 [0360]



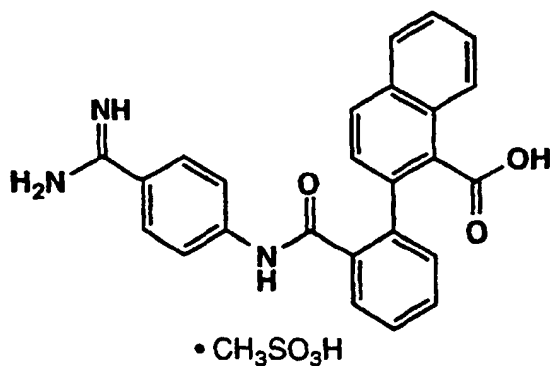
TLC : Rf 0.24 (Chloroform : Methanol : Acetic acid = 4 : 1 : 0.1) ;

NMR (d₆-DMSO) : δ 13.4-12.0 (1H, br), 10.36 (1H, s), 9.14 (2H, s), 8.83 (2H, s), 7.7-7.6 (3H, m), 7.44 (1H, s), 7.4-7.2 (2H, m), 7.2-7.0 (4H, m), 3.78 (3H, s), 2.42 (3H, s), 2.37 (3H, s).

Example 19(21)

2-(2-(4-amidinophenylcarbamoyl)phenyl)-1-naphthalenecarboxylic acid methanesulfonate

35 [0361]



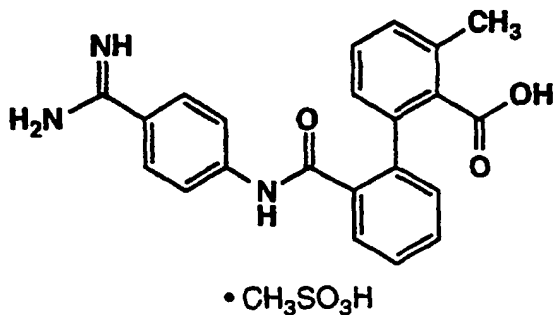
TLC : Rf 0.40 (Chloroform : Methanol : Water = 7 : 3 : 0.3) ;

NMR (d₆-DMSO) : δ 10.50 (1H, br.s), 9.12 (2H, s), 8.83 (2H, s), 7.93-8.00 (3H, m), 7.58-7.79 (9H, m), 7.42 (1H, m), 7.37 (1H, d, J = 8.4 Hz), 2.35 (3H, s).

Example 19(22)

2'-(4-amidinophenylcarbamoyl)-3-methyl-2-biphenylcarboxylic acid methanesulfonate

[0362]



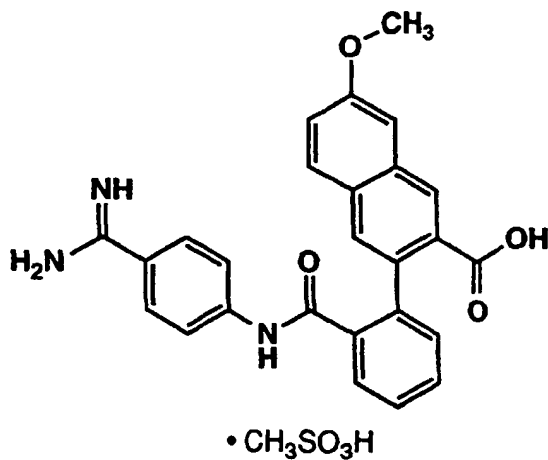
TLC : Rf 0.19 (Chloroform : Methanol : Acetic acid = 4 : 1 : 0.1) ;

NMR (d₆-DMSO) : δ 13.7-12.7 (1H, br), 10.29 (1H, s), 9.16 (2H, s), 8.83 (2H, s), 7.74 (2H, d, J = 8.8 Hz), 7.59 (2H, d, J = 8.8 Hz), 7.8-7.6 (1H, m), 7.6-7.5 (2H, m), 7.4-7.2 (1H, m), 7.25 (2H, d, J = 7 Hz), 7.03 (1H, dd, J = 7.4, 2 Hz), 2.37 (3H, s), 2.34 (3H, s).

Example 19(23)

3-(2-(4-amidinophenylcarbamoyl)phenyl)-7-methoxy-2-naphthalenecarboxylic acid methanesulfonate

[0363]



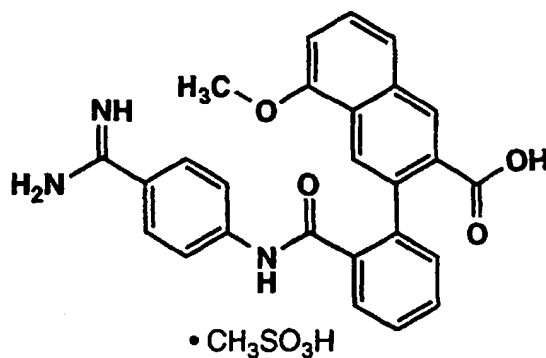
TLC : Rf 0.61 (Ethyl acetate : Acetic acid : Water = 3 : 1 : 0.5) ;

NMR (d₆-DMSO) : δ 12.84 (1H, br.s), 10.40 (1H, s), 9.09 (2H, br.s), 8.78 (2H, br.s), 8.35 (1H, s), 7.84 (1H, d, J = 9.4 Hz), 7.7-7.4 (9H, m), 7.34 (1H, dd, J = 7.2, 1.4 Hz), 7.26 (1H, dd, J = 9.4, 2.4 Hz), 3.87 (3H, s), 2.32 (3H, s).

Example 19(24)

3-(2-(4-amidinophenylcarbamoyl)phenyl)-5-methoxy-2-naphthalenecarboxylic acid methanesulfonate

5 [0364]

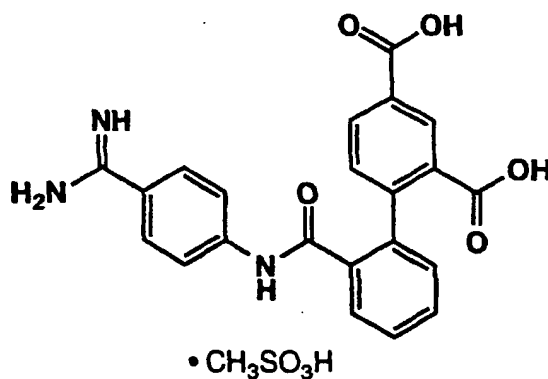
TLC : R_f 0.29 (Chloroform : Methanol : Water = 10 : 3 : 0.2) ;

25 NMR (d₅-DMSO) : δ 12.88 (1H, br.s), 10.49 (1H, s), 9.10 (2H, br.s), 8.79 (2H, br.s), 8.40 (1H, s), 7.94 (1H, s), 7.8-7.4 (9H, m), 7.34 (1H, dd, J = 2.0, 6.8 Hz), 7.07 (1H, d, J = 7.4 Hz), 3.91 (3H, s), 2.32 (3H, s).

Example 19(25)

30 2'-(4-amidinophenylcarbamoyl)-2, 4-biphenyldicarboxylic acid methanesulfonate

[0365]

TLC : R_f 0.22 (Chloroform : Methanol : Water = 6 : 4 : 1) ;

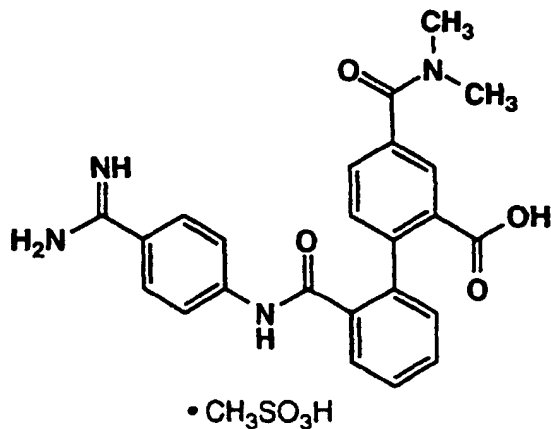
50 NMR (d₆-DMSO) : δ 13.02 (1H, br.s), 10.54 (1H, s), 9.16 (2H, s), 8.89 (2H, s), 8.38 (1H, d, J = 2.0 Hz), 8.05 (1H, dd, J = 2.0, 7.8 Hz), 7.74 (4H, s), 7.73 (1H, dd, J = 2.6, 7.8 Hz), 7.53-7.60 (2H, m), 7.37 (1H, d, J = 7.8 Hz), 7.29 (1H, dd, J = 2.6, 7.8 Hz), 2.38 (3H, s).

55

Example 19(26)

2'-(4-amidinophenylcarbamoyl)-4-dimethylcarbamoyl-2-biphenylcarboxylic acid methanesulfonate

[0366]



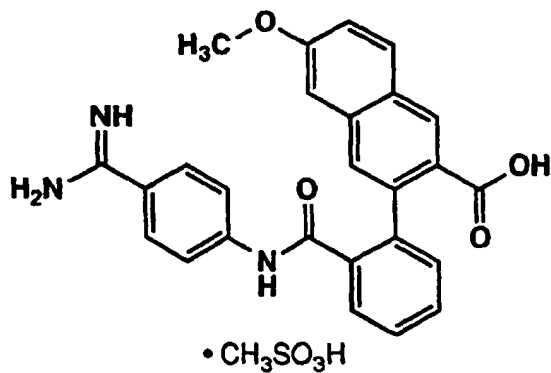
TLC : Rf 0.46 (Chloroform : Methanol : Water = 7 : 3 : 0.3) ;

NMR (d₆-DMSO) : δ 10.43 (1H, s), 9.16 (2H, s), 8.88 (2H, s), 7.67-7.80 (6H, m), 7.52-7.59 (3H, m), 7.31 (2H, d, J = 7.8 Hz), 2.98 (3H, br.s), 2.85 (3H, br.s), 2.37 (3H, s).

Example 19(27)

3-(2-(4-amidinophenylcarbamoyl)phenyl)-6-methoxy-2-naphthalenecarboxylic acid methanesulfonate

[0367]



TLC : Rf 0.51 (Chloroform : Methanol : Water = 10 : 3 : 0.2) ;

NMR (d₆-DMSO) : δ 13.0-12.0 (1H, br), 11.5-10.5 (1H, br), 9.05 (2H, br.s), 8.85 (2H, br.s), 8.29 (1H, s), 7.93 (1H, d, J = 8.8 Hz), 7.7-7.5 (5H, m), 7.6-7.4 (3H, m), 7.4-7.1 (3H, m), 3.84 (3H, s), 2.30 (3H, s).

Example 19(28)

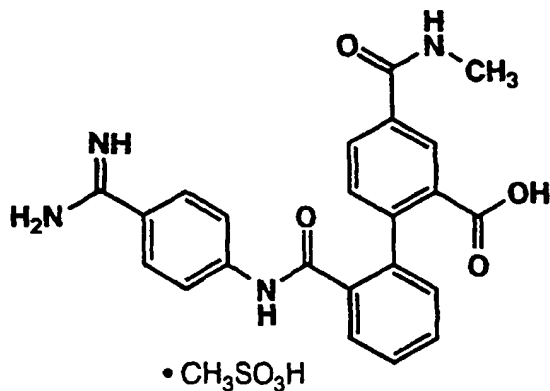
2'-(4-amidinophenylcarbamoyl)-4-methylcarbamoyl-2-biphenylcarboxylic acid methanesulfonate

5 [0368]

10

15

20



25

TLC : Rf 0.27 (Chloroform : Methanol : Water = 7 : 3 : 0.3) ;
 NMR (d₆-DMSO) : δ 10.49 (1H, s), 9.16 (2H, s), 8.89 (2H, s), 8.62 (1H, br.q, J = 4.6 Hz), 8.30 (1H, d, J = 1.8 Hz),
 7.96 (1H, dd, J = 1.8, 8.2 Hz), 7.76 (2H, d, J = 9.0 Hz), 7.71 (2H, d, J = 9.0 Hz), 7.70 (1H, dd, J = 2.0, 7.6 Hz), 7.52-
 7.58 (2H, m), 7.33 (1H, d, J = 8.2 Hz), 7.28 (1H, dd, J = 2.0, 7.6 Hz), 2.79 (3H, br.d, J = 4.6 Hz), 2.39 (3H, s).

30 Example 19(29)

3-(2-(4-amidinophenylcarbamoyl)phenyl)-8-methoxy-2-naphthalenecarboxylic acid methanesulfonate

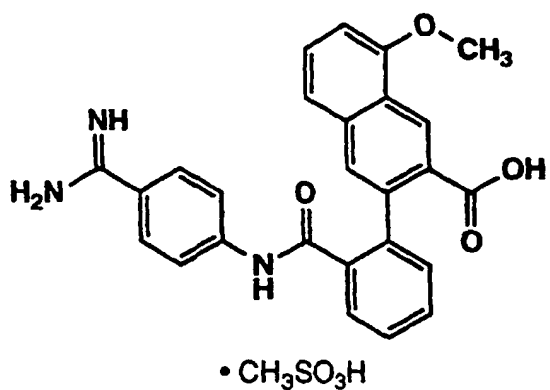
35 [0369]

35

40

45

50



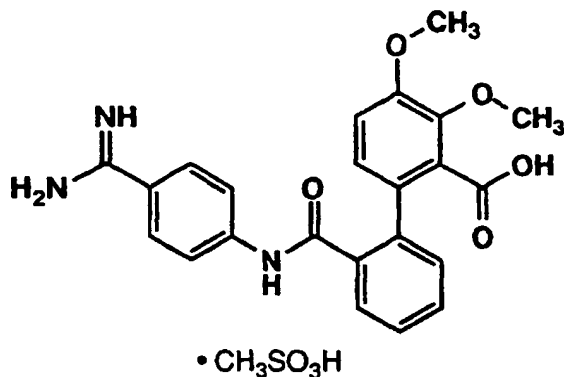
55

TLC : Rf 0.26 (Chloroform : Methanol : Water = 10 : 3 : 0.2) ;
 NMR (d₆-DMSO) : δ 12.76 (1H, br.s), 10.45 (1H, s), 9.09 (2H, br.s), 8.80 (2H, br.s), 8.68 (1H, s), 7.8-7.5 (10H, m),
 7.35 (1H, m), 7.04 (1H, m), 4.00 (3H, s), 2.33 (3H, s).

Example 19(30)

2'-(4-amidinophenylcarbamoyl)-3, 4-dimethoxy-2-biphenylcarboxylic acid methanesulfonate

[0370]



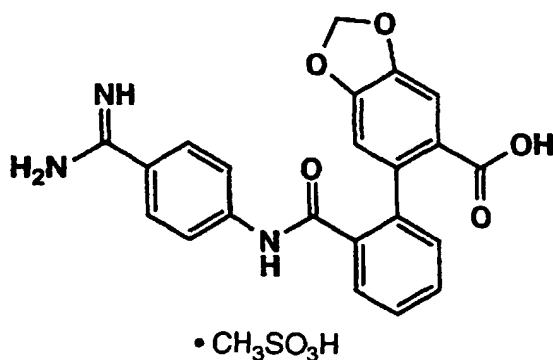
TLC : Rf 0.16 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d₆-DMSO) : δ 13.7-13.2 (1H, broad), 10.30 (1H, s), 9.16 (2H, brs), 8.89 (2H, brs), 7.76 (2H, d, J = 9.0 Hz), 7.69-7.62 (3H, m), 7.58-7.46 (2H, m), 7.33-7.27 (1H, m), 7.07 (1H, d, J = 8.5 Hz), 6.92 (1H, d, J = 8.5 Hz), 3.79 (3H, s), 3.77 (3H, s), 2.35 (3H, s).

Example 19(31)

6-(2-(4-amidinophenylcarbamoyl)phenyl)-1,2-methylenedioxybenzen-5-carboxylic acid methanesulfonate

[0371]



TLC : Rf 0.22 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d₆-DMSO) : δ 12.8-12.2 (1H, broad), 10.39 (1H, s), 9.16 (2H, brs), 8.88 (2H, brs), 7.76 (2H, d, J = 9.0 Hz), 7.70 (2H, d, J = 9.0 Hz), 7.65-7.60 (1H, m), 7.56-7.42 (2H, m), 7.30 (1H, s), 7.24-7.19 (1H, m), 6.75 (1H, s), 6.10 (2H, s), 2.34 (3H, s).

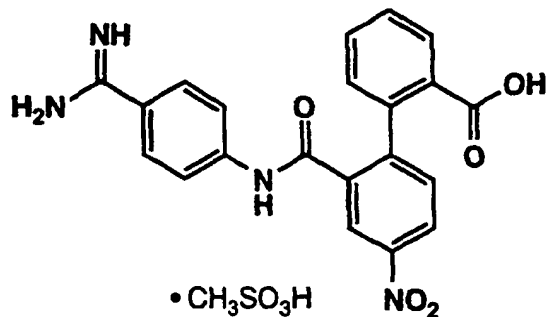
Example 19(32)

2'-(4-amidinophenylcarbamoyl)-4'-nitro-2-biphenylcarboxylic acid methanesulfonate

5 [0372]

10

15



20

TLC : R_f 0.21 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

25

NMR (d₆-DMSO) : δ 13.0-12.5 (1H, broad), 10.77 (1H, s), 9.16 (2H, brs), 8.88 (2H, brs), 8.49 (1H, d, J = 2.5 Hz), 8.39 (1H, dd, J = 8.5 Hz, 2.5 Hz), 7.91 (1H, dd, J = 8.0 Hz, 1.5 Hz), 7.76 (2H, d, J = 9.0 Hz), 7.69 (2H, d, J = 9.0 Hz), 7.59 (1H, td, J = 8.0 Hz, 1.5 Hz), 7.58 (1H, d, J = 8.5 Hz), 7.48 (1H, d, J = 8.0 Hz, 1.5 Hz), 7.28 (1H, dd, J = 8.0 Hz, 1.5 Hz), 2.34 (3H, s).

Example 19(33)

30

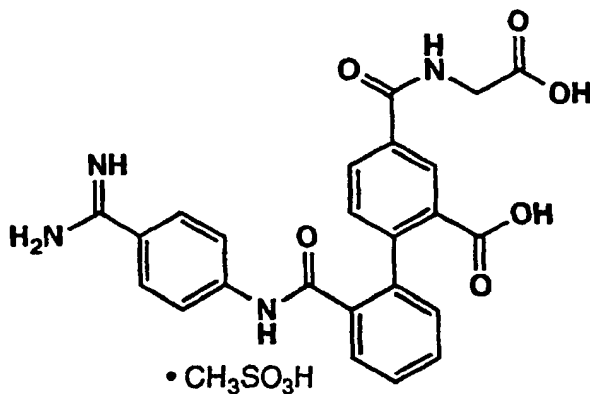
2'-(4-amidinophenylcarbamoyl)-4'-((carboxymethyl)carbamoyl)-2-biphenylcarboxylic acid methanesulfonate

[0373]

35

40

45



50

TLC : R_f 0.28 (Chloroform : Methanol : Water = 6 : 4 : 1) ;

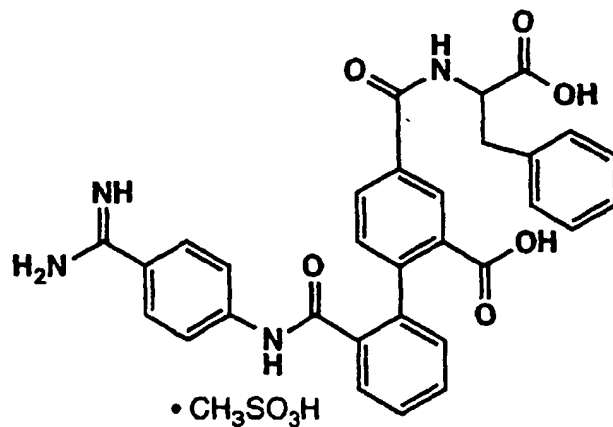
55

NMR (d₆-DMSO) : δ 10.54 (1H, s), 9.22 (2H, s), 9.07 (1H, br.t, J = 5.6 Hz), 9.01 (2H, s), 8.35 (1H, d, J = 1.2 Hz), 8.01 (1H, dd, J = 1.2, 7.6 Hz), 7.70-7.75 (5H, m), 7.50-7.62 (2H, m), 7.36 (1H, d, J = 7.6 Hz), 7.30 (1H, d, J = 7.6 Hz), 3.94 (2H, d, J = 5.6 Hz), 2.42 (3H, s).

Example 19(34)

2'-(4-amidinophenylcarbamoyl)-4-((1-carboxy-2-phenylethyl)carbamoyl)-2-biphenylcarboxylic acid methanesulfonate

5 [0374]



25

TLC : Rf 0.20 (Chloroform : Methanol : Water = 7 : 3 : 0.3) ;

NMR (d₆-DMSO) : δ 10.53 (1H, s), 9.17 (2H, s), 8.95 (1H, d, J = 5.0 Hz), 8.92 (2H, s), 8.28 (1H, d, J = 1.6 Hz), 7.92 (1H, dd, J = 1.6, 8.0 Hz), 7.69-7.74 (5H, m), 7.53-7.58 (2H, m), 7.17-7.35 (7H, m), 4.64 (1H, m), 3.01-3.26 (2H, m), 2.39 (3H, s).

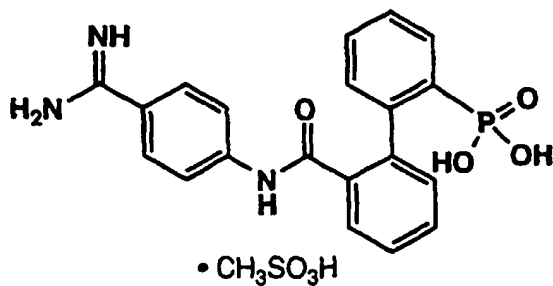
30

Example 19(35)

2'-(4-amidinophenylcarbamoyl)-2-biphenylphosphoric acid methanesulfonate

35

[0375]



40

45

50

TLC : Rf 0.10 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d₆-DMSO) : δ 11.37 (1H, s), 9.10 (2H, brs), 8.85 (2H, brs), 7.87-7.74 (1H, m), 7.65 (2H, d, J = 9.0 Hz), 7.59 (2H, d, J = 9.0 Hz), 7.60-7.30 (5H, m), 7.26 (1H, dd, J = 6.0 Hz, 3.0 Hz), 7.05-6.97 (1H, m), 2.33 (3H, s).

55

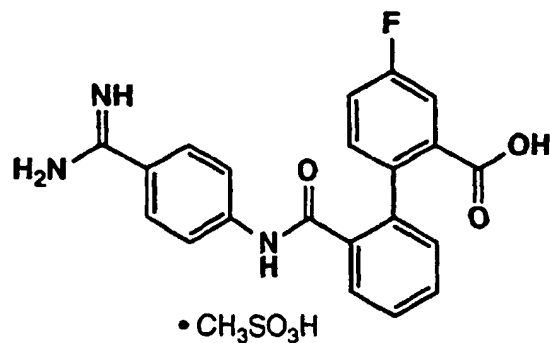
Example 19(36)

2'-(4-amidinophenylcarbamoyl)-4-fluoro-2-biphenylcarboxylic acid methanesulfonate

5 [0376]

10

15



20

TLC : Rf 0.45 (Chloroform : Methanol : Water = 7 : 3 : 0.3) ;

25 NMR (d₆-DMSO) : δ 10.45 (1H, s), 9.16 (2H, s), 8.84 (2H, s), 7.73 (4H, s), 7.67 (1H, dd, J = 2.6, 8.0 Hz), 7.50-7.61 (3H, m), 7.39 (1H, dt, J = 2.6, 8.0 Hz), 7.25-7.32 (2H, m), 2.36 (3H, s).

Example 19(37)

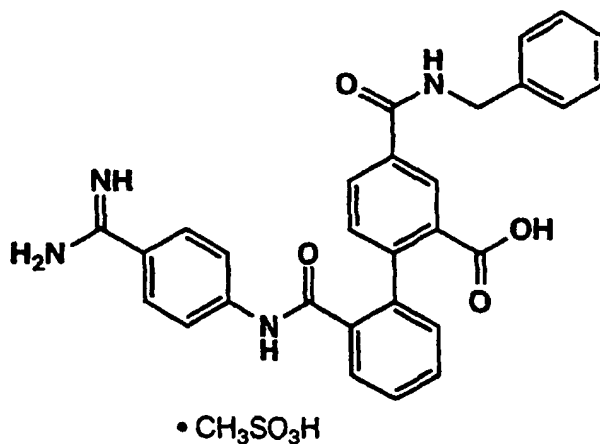
30 2'-(4-amidinophenylcarbamoyl)-4-benzylcarbamoyl-2-biphenylcarboxylic acid methanesulfonate

[0377]

35

40

45



50

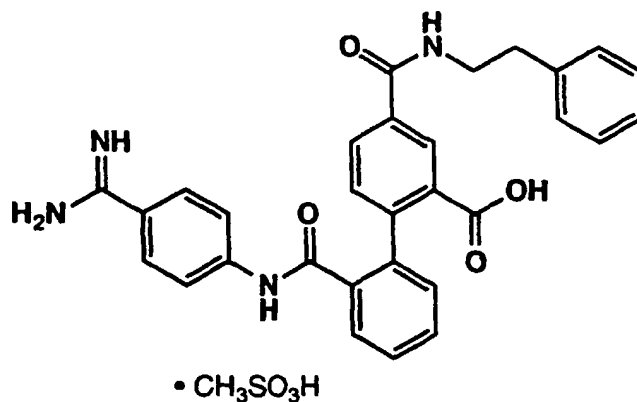
TLC : Rf 0.70 (Chloroform : Methanol : Water = 7 : 3 : 0.3) ;

55 NMR (d₆-DMSO) : δ 10.54 (1H, s), 9.26 (1H, br.t, J = 5.8 Hz), 9.17 (2H, s), 8.90 (2H, s), 8.37 (1H, d, J = 1.8 Hz), 8.03 (1H, dd, J = 1.8, 8.0 Hz), 7.74 (4H, s), 7.71 (1H, dd, J = 1.8, 8.0 Hz), 7.53-7.59 (2H, m), 7.24-7.37 (7H, m), 4.48 (2H, d, J = 5.8 Hz), 2.34 (3H, s).

Example 19(38)

2'-(4-amidinophenylcarbamoyl)-4-phenylethylcarbamoyl-2-biphenylcarboxylic acid methanesulfonate

[0378]



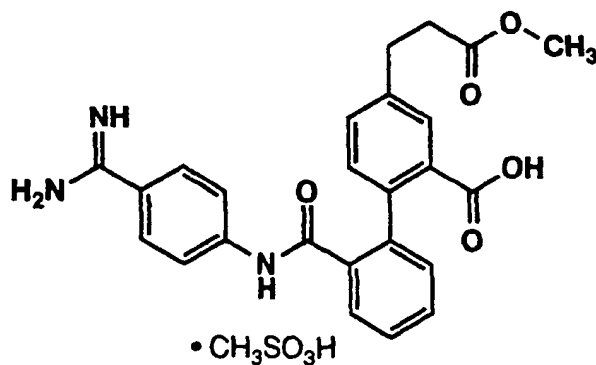
TLC : Rf 0.56 (Chloroform : Methanol : Water = 7 : 3 : 0.3) ;

NMR (d₆-DMSO) : δ 10.52 (1H, s), 9.15 (2H, s), 8.83 (2H, s), 8.77 (1H, br.t, J = 5.8 Hz), 8.30 (1H, d, J = 1.8 Hz), 7.95 (1H, dd, J = 1.8, 8.0 Hz), 7.73 (4H, s), 7.70 (1H, dd, J = 1.8, 8.0 Hz), 7.52-7.59 (2H, m), 7.19-7.35 (7H, m), 3.50 (2H, m), 2.85 (2H, t, J = 7.0 Hz), 2.34 (3H, s).

Example 19(39)

2'-(4-amidinophenylcarbamoyl)-4-(2-methoxycarbonyl)ethyl-2-biphenylcarboxylic acid methanesulfonate

[0379]



TLC : Rf 0.24 (Chloroform : Methanol = 4 : 1) ;

NMR (d₆-DMSO) : δ 13.0-12.5 (1H, br), 10.41 (1H, s), 9.14 (2H, s), 8.82 (2H, s), 7.8-7.6 (6H, m), 7.6-7.4 (2H, m), 7.38-7.34 (1H, m), 7.25-7.21 (1H, m), 7.14 (1H, d, J = 7.8 Hz), 3.56 (3H, s), 2.89 (2H, t, J = 6.8 Hz), 2.64 (2H, t, J = 6.8 Hz), 2.34 (3H, s).

Example 19(40)

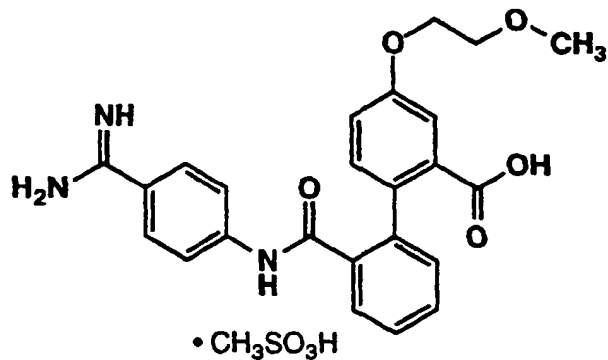
2'-(4-amidinophenylcarbamoyl)-4-(2-methoxyethoxy)-2-biphenylcarboxylic acid methanesulfonate

5 [0380]

10

15

20



25

TLC : R_f 0.42 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;
 NMR (d₆-DMSO) : δ 13.8-12.5 (1H, br), 10.37 (1H, s), 9.13 (2H, br.s), 8.79 (2H, br.s), 7.80-7.55 (5H, m), 7.55-7.40 (2H, s), 7.30 (1H, d, J = 2.4 Hz), 7.80-7.00 (3H, m), 4.11 (2H, t, J = 4.4 Hz), 3.64 (2H, t, J = 4.4 Hz), 3.28 (3H, s), 2.31 (3H, s).

30

Example 19(41)

2'-(4-amidinophenylcarbamoyl)-4-((2-methylpropyl)carbamoyl)-2-biphenylcarboxylic acid methanesulfonate

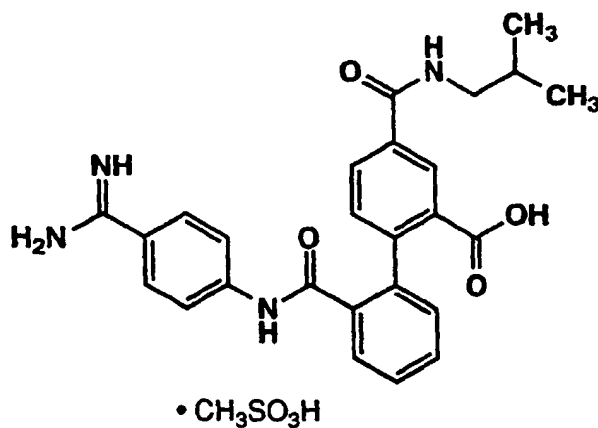
35 [0381]

35

40

45

50



55

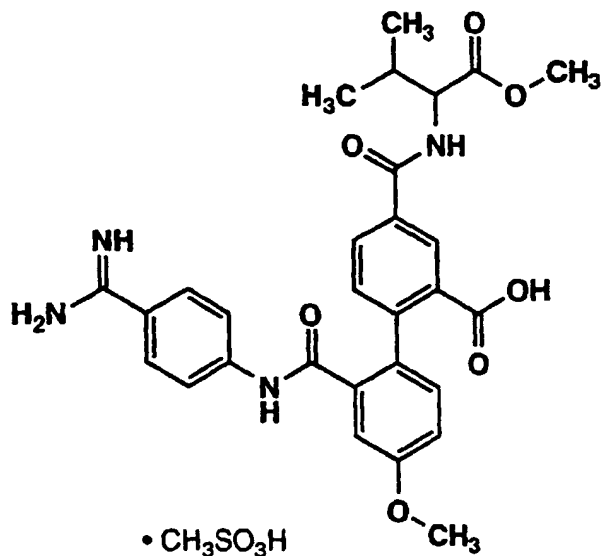
TLC : R_f 0.26 (Chloroform : Methanol : Water = 8 : 2 : 0.2) ;
 NMR (d₆-DMSO) : δ 10.53 (1H, s), 9.15 (2H, s), 8.85 (2H, s), 8.65 (1H, br.t, J = 6.8 Hz), 8.31 (1H, d, J = 1.8 Hz), 7.97 (1H, dd, J = 1.8, 7.8 Hz), 7.74 (4H, s), 7.70 (1H, dd, J = 1.8, 7.8 Hz), 7.52-7.59 (2H, m), 7.33 (1H, d, J = 7.8 Hz),

7.28 (1H, dd, J = 1.8, 7.8 Hz), 3.09 (2H, br.t, J = 6.8 Hz), 2.35 (3H, s), 1.85 (1H, m), 0.89 (6H, d, J = 6.8 Hz).

Example 19(42)

- 5 2'-{(4-amidinophenylcarbamoyl)-4'-methoxy-4-((1-methoxycarbonyl-2-methylpropyl)carbamoyl)-2-biphenylcarboxylic acid methanesulfonate

[0382]



TLC : R_f 0.61 (Chloroform : Methanol : Water = 7 : 3 : 0.3) ;

NMR (d₆-DMSO) : δ 10.53 (1H, s), 9.14 (2H, s), 8.82 (1H, d, J = 7.8 Hz), 8.77 (2H, s), 8.31 (1H, d, J = 1.6 Hz), 7.99 (1H, dd, J = 1.6, 8.0 Hz), 7.74 (4H, s), 7.32 (1H, d, J = 8.0 Hz), 7.24 (1H, m), 7.13-7.19 (2H, m), 4.31 (1H, t, J = 7.8 Hz), 3.89 (3H, s), 3.66 (3H, s), 2.32 (3H, s), 2.18 (1H, m), 0.98 (3H, d, J = 6.6 Hz), 0.94 (3H, d, J = 6.6 Hz).

Example 19(43)

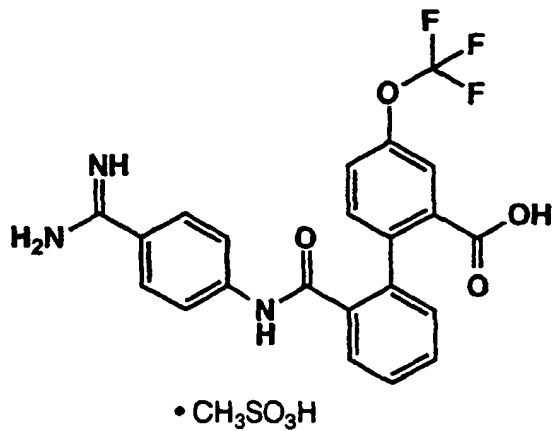
2'-(4-amidinophenylcarbamoyl)-4-trifluoromethoxy-2-biphenylcarboxylic acid methanesulfonate

5 [0383]

10

15

20



25

30

TLC : R_f 0.25 (Chloroform : Methanol : Water = 8 : 2 : 0.2) ;NMR (d₆-DMSO) : δ 10.5 (1H, s), 9.15 (2H, br s), 8.84 (2H, br s), 7.74-7.69 (6H, m), 7.59-7.53 (3H, m), 7.38 (1H, d, J = 8.4 Hz), 7.33-7.28 (1H, m), 2.37 (3H, s).

35

40

45

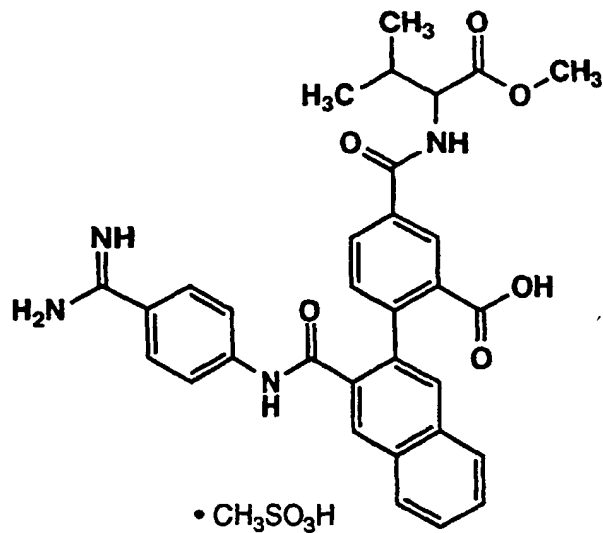
50

55

Example 19(44)

2-(3-(4-amidinophenylcarbamoyl)naphthalen-2-yl)-5-((1-methoxycarbonyl-2-methylpropyl)carbamoyl)benzoic acid methanesulfonate

[0384]



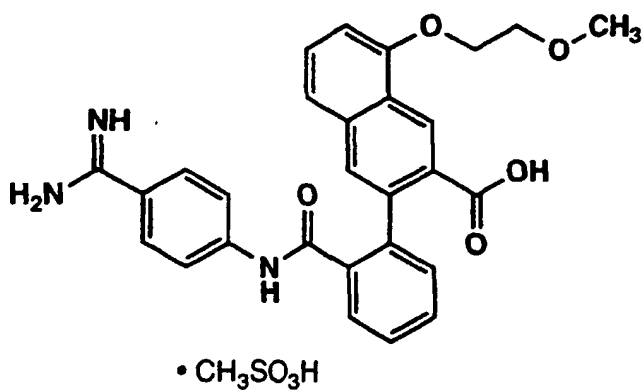
TLC : R_f 0.48 (Chloroform : Methanol : Water = 8 : 2 : 0.2) ;

NMR (d₆-DMSO) : δ 10.78 (1H, s), 9.18 (2H, s), 8.89 (1H, d, J = 7.6 Hz), 8.87 (2H, s), 8.40 (1H, d, J = 1.8 Hz), 8.33 (1H, s), 8.01-8.14 (3H, m), 7.74-7.85 (5H, m), 7.64-7.69 (2H, m), 7.46 (1H, d, J = 8.0 Hz), 4.34 (1H, t, J = 7.6 Hz), 3.68 (3H, s), 2.35 (3H, s), 2.23 (1H, m), 1.00 (3H, d, J = 7.0 Hz), 0.96 (3H, d, J = 7.0 Hz).

Example 19(45)

3-(2-(4-amidinophenylcarbamoyl)phenyl)-8-(2-methoxyethoxy)-2-naphthalenecarboxylic acid methanesulfonate

[0385]



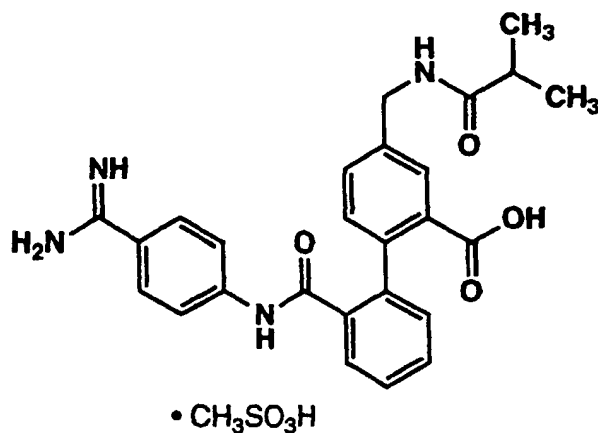
TLC : Rf 0.61 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d_6 -DMSO) : δ 13.1-12.0 (1H, br), 10.44 (1H, s), 9.09 (2H, brs), 8.80 (2H, brs), 8.67 (1H, s), 7.70 (1H, s), 7.67 (4H, likes), 7.7-7.4 (5H, m), 7.36 (1H, brd, J = 7.8 Hz), 7.05 (1H, brd, J = 5.4 Hz), 4.4-4.2 (2H, m), 3.9-3.7 (2H, m), 3.36 (3H, s), 2.32 (3H, s).

Example 19(46)

2'-(4-amidinophenylcarbamoyl)-4-((isopropylcarbonyl)aminomethyl)-2-biphenylcarboxylic acid methanesulfonate

[0386]



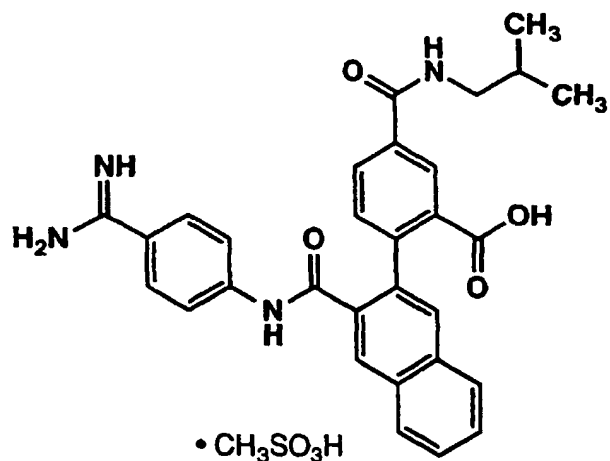
TLC : Rf 0.54 (Chloroform : Methanol : Water = 8 : 2 : 0.1) ;

NMR (d_6 -DMSO) : δ 10.5 (1H, s), 9.17 (2H, br s), 8.87 (2H, br s), 8.35 (1H, t, J = 6.6 Hz), 7.78-7.64 (6H, m), 7.55-7.48 (2H, m), 7.36 (1H, dd, J = 1.8, 8.0 Hz), 7.24-7.16 (2H, m), 4.30 (2H, d, J = 6.0 Hz), 2.52-2.41 (1H, m), 2.36 (3H, s), 1.04 (6H, d, J = 7.0 Hz).

Example 19(47)

2-(3-(4-amidinophenylcarbamoyl)naphthalen-2-yl)-5-((2-methylpropyl)carbamoyl)benzoic acid methanesulfonate

[0387]

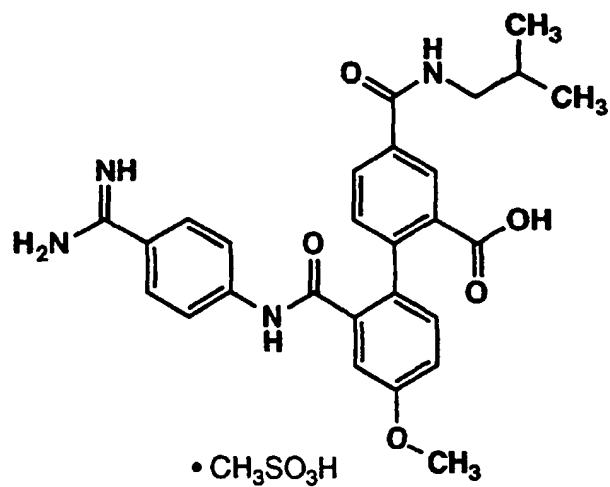
TLC : R_f 0.74 (Chloroform : Methanol : Water = 7 : 3 : 0.3) ;

NMR (d₆-DMSO) : δ 10.76 (1H, s), 9.18 (2H, s), 8.86-8.93 (3H, m), 8.68 (1H, br.t, J = 6.6 Hz), 8.36 (1H, s), 8.32 (1H, s), 8.00-8.14 (3H, m), 7.79 (4H, s), 7.63-7.68 (2H, m), 7.44 (1H, d, J = 8.0 Hz), 3.11 (2H, br.t, J = 6.6 Hz), 2.36 (3H, s), 1.88 (1H, m), 0.91 (6H, d, J = 6.6 Hz).

Example 19(48)

2'-(4-amidinophenylcarbamoyl)-4'-methoxy-4-((2-methylpropyl)carbamoyl)-2-biphenylcarboxylic acid methanesulfonate

[0388]

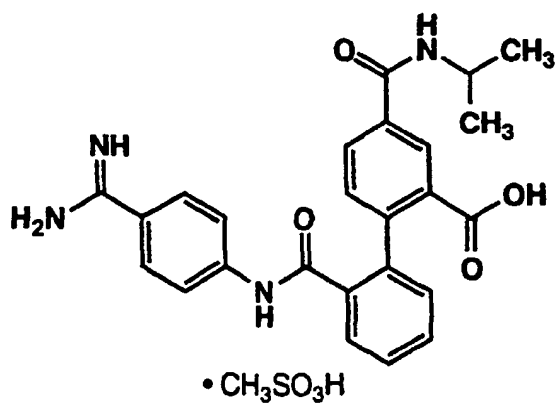


TLC : R_f 0.62 (Chloroform : Methanol : Water = 7 : 3 : 0.3) ;
 NMR (d₆-DMSO) : δ 10.51 (1H, s), 9.14 (2H, s), 8.83 (2H, s), 8.63 (1H, br.t, J = 6.6 Hz), 8.28 (1H, d, J = 2.0 Hz), 7.95 (1H, dd, J = 2.0, 8.0 Hz), 7.74 (4H, s), 7.30 (1H, d, J = 8.0 Hz), 7.24 (1H, d, J = 2.0 Hz), 7.21 (1H, d, J = 8.0 Hz), 7.14 (1H, dd, J = 2.0, 8.0 Hz), 3.89 (3H, s), 3.09 (2H, t, J = 6.6 Hz), 2.35 (3H, s), 1.85 (1H, m), 0.89 (6H, d, J = 7.0 Hz).

Example 19(49)

2'-(4-amidinophenylcarbamoyl)-4-isopropylcarbamoyl-2-biphenylcarboxylic acid methanesulfonate

[0389]



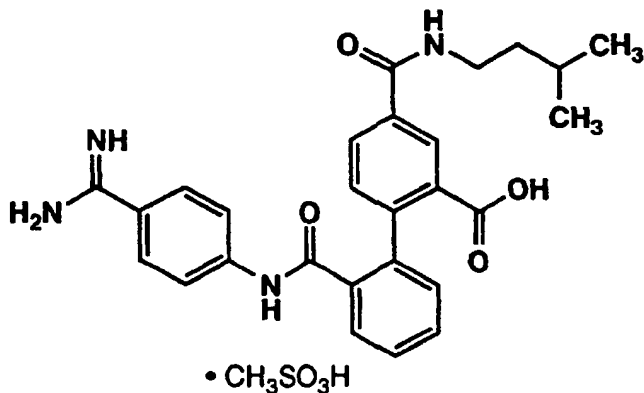
TLC : Rf 0.33 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d_6 -DMSO) : δ 10.5 (1H, s), 9.16 (2H, br s), 8.86 (2H, br s), 8.43 (1H, d, J = 7.6 Hz), 8.30 (1H, d, J = 1.6 Hz),
 7.97 (1H, dd, J = 1.6, 8.0 Hz), 7.73-7.68 (5H, m), 7.59-7.52 (2H, m), 7.34-7.25 (2H, m), 4.20-4.02 (1H, m), 2.34
 (3H, s), 1.17 (6H, d, J = 6.6 Hz).

Example 19(50)

2'-(4-amidinophenylcarbamoyl)-4-((3-methylbutyl)carbamoyl)-2-biphenylcarboxylic acid methanesulfonate

[0390]



TLC : Rf 0.42 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d_6 -DMSO) : δ 10.5 (1H, s), 9.14 (2H, br s), 8.83 (2H, br s), 8.61 (1H, t, J = 6.0 Hz), 8.30 (1H, d, J = 1.6 Hz),
 7.96 (1H, dd, J = 1.6, 8.0 Hz), 7.73-7.68 (5H, m), 7.62-7.53 (2H, m), 7.35-7.26 (2H, m), 3.34-3.24 (2H, m), 2.37 (3H,
 s), 1.69-1.53 (1H, m), 1.48-1.37 (2H, m), 0.90 (6H, d, J = 6.2 Hz).

Example 19(51)

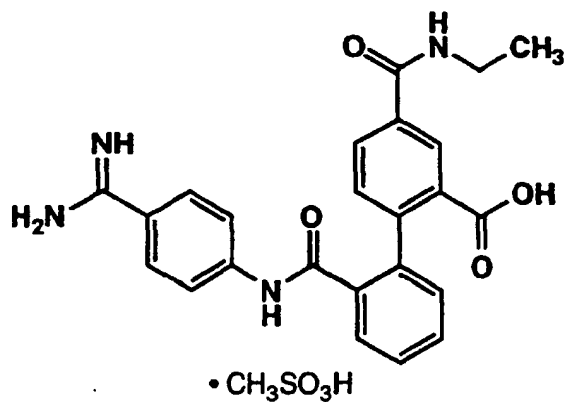
2'-(4-amidinophenylcarbamoyl)-4-ethylcarbamoyl-2-biphenylcarboxylic acid methanesulfonate

5 [0391]

10

15

20



25

TLC : R_f 0.10 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d₆-DMSO) : δ 10.5 (1H, s), 9.17 (2H, br s), 8.86 (2H, br s), 8.66 (1H, t, J = 5.4 Hz), 8.30 (1H, d, J = 1.8 Hz), 7.97 (1H, dd, J = 1.8, 7.6 Hz), 7.73-7.68 (5H, m), 7.59-7.52 (2H, m), 7.35-7.26 (2H, m), 3.36-3.23 (2H, m), 2.36 (3H, s), 1.13 (3H, t, J = 7.0 Hz).

30

Example 19(52)

2'-(4-amidinophenylcarbamoyl)-4-butylcarbamoyl-2-biphenylcarboxylic acid methanesulfonate

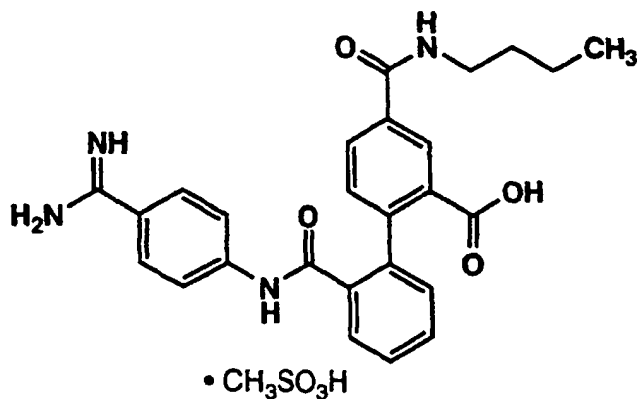
35

[0392]

40

45

50



55

TLC : R_f 0.26 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

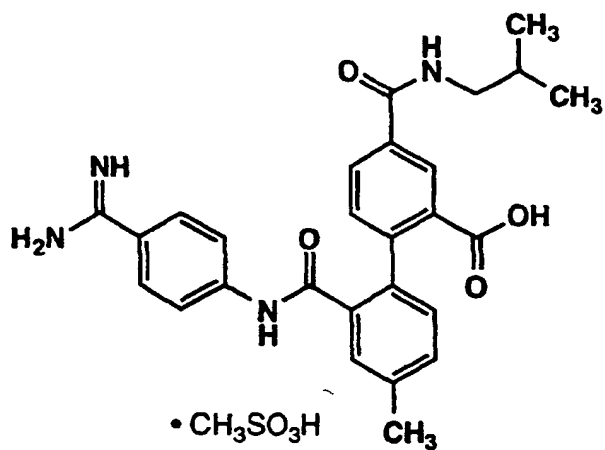
NMR (d₆-DMSO) : δ 10.5 (1H, s), 9.16 (2H, brs), 8.85 (2H, brs), 8.63 (1H, t, J = 5.4 Hz), 8.30 (1H, d, J = 1.6 Hz),

7.97 (1H, dd, $J = 1.6, 8.2$ Hz), 7.73-7.68 (5H, m), 7.58-7.53 (2H, m), 7.35-7.26 (2H, m), 3.32-3.22 (2H, m), 1.55-1.24 (4H, m), 2.36 (3H, s), 0.90 (3H, t, $J = 7.2$ Hz).

Example 19(53)

2'-(4-amidinophenylcarbamoyl)-4'-methyl-4-((2-methylpropyl)carbamoyl)-2-biphenylcarboxylic acid methanesulfonate

[0393]



TLC : R_f 0.33 (Chloroform : Methanol : Water = 8 : 2 : 0.2) ;

NMR (d₆-DMSO) : δ 10.51 (1H, s), 9.15 (2H, br.s), 8.83 (2H, br.s), 8.63 (1H, t, $J = 6.2$ Hz), 8.29 (1H, d, $J = 1.8$ Hz), 7.95 (1H, dd, $J = 1.8, 8.0$ Hz), 7.73 (4H, s), 7.51 (1H, s), 7.38 (1H, d, $J = 8.0$ Hz), 7.29 (1H, d, $J = 8.0$ Hz), 7.16 (1H, d, $J = 8.0$ Hz), 3.09 (2H, t, $J = 6.2$ Hz), 2.45 (3H, s), 2.36 (3H, s), 1.86 (1H, m), 0.89 (6H, d, $J = 6.6$ Hz).

Example 19(54)

2'-(4-amidinophenylcarbamoyl)-4-((cyclohexylmethyl)carbamoyl)-2-biphenylcarboxylic acid methanesulfonate

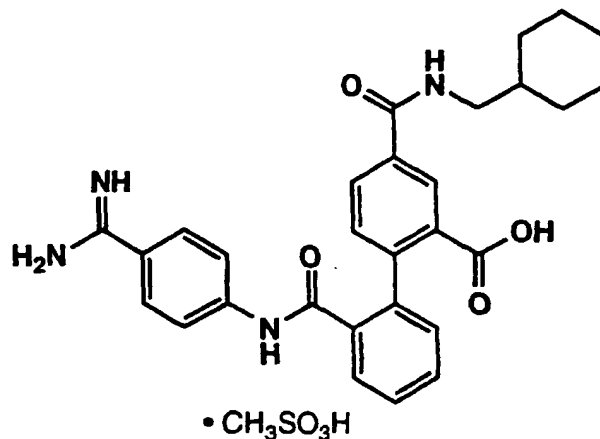
5 [0394]

10

15

20

25

TLC : R_f 0.40 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

30 NMR (d₆-DMSO) : δ 10.5 (1H, s), 9.17 (2H, br s), 8.87 (2H, br s), 8.60 (1H, t, J = 5.4 Hz), 8.30 (1H, d, J = 1.6 Hz),
 7.97 (1H, dd, J = 1.6, 8.0 Hz), 7.74-7.69 (5H, m), 7.62-7.50 (2H, m), 7.34-7.26 (2H, m), 3.11 (1H, t, J = 5.8 Hz),
 2.36 (3H, s), 1.80-1.40 (6H, m), 1.30-0.75 (5H, m).

Example 19(55)

35 2'-(4-amidinophenylcarbamoyl)-4-((5-(t-butoxycarbonylamino)pentyl) carbamoyl)-2-biphenylcarboxylic acid methanesulfonate

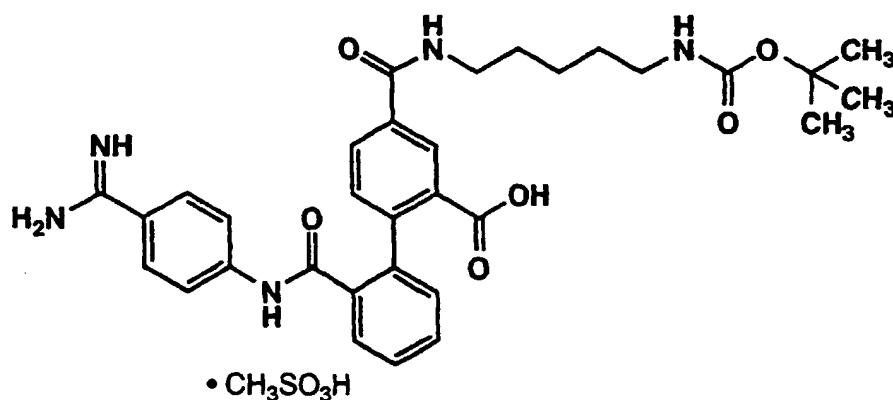
[0395]

40

45

50

55



EP 1 078 917 A1

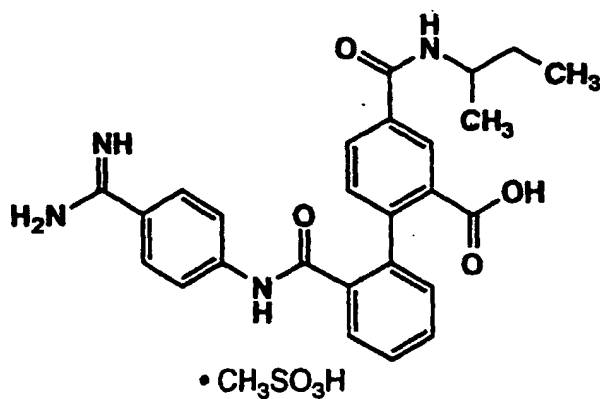
TLC : Rf 0.39 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d₆-DMSO) : δ 10.5 (1H, d, J = 5.8 Hz), 9.17 (2H, br s), 8.86 (2H, m), 8.65 (1H, t, J = 5.8 Hz), 8.30 (1H, s), 8.00-7.95 (1H, m), 7.74-7.60 (4H, m), 7.60-7.50 (2H, m), 7.35-7.25 (2H, m), 6.75 (1H, br s), 3.40- 3.20 (2H, m), 3.00-2.70 (2H, m), 2.34 (3H, s), 1.60-1.20 (6H, m), 1.36 (9H, s).

Example 19(56)

2'-(4-amidinophenylcarbamoyl)-4-((1-methylpropyl)carbamoyl)-2-biphenylcarboxylic acid methanesulfonate

[0396]



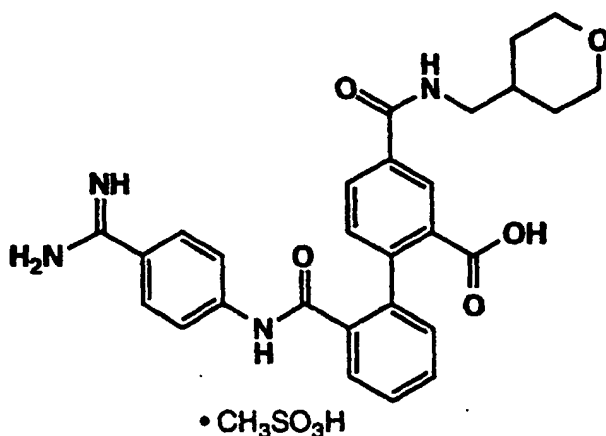
TLC : Rf 0.23 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d₆-DMSO) : δ 10.5 (1H, s), 9.18 (2H, br s), 8.89 (2H, br s), 8.36 (1H, d, J = 8.2 Hz), 8.31 (1H, d, J = 1.8 Hz), 7.98 (1H, dd, J = 1.8, 8.2 Hz), 7.74-7.69 (4H, m), 7.59-7.52 (2H, m), 7.32 (1H, d, J = 8.2 Hz), 7.30-7.26 (1H, m), 4.10-3.90 (1H, m), 2.37 (3H, s), 1.56-1.48 (2H, m), 1.14 (3H, d, J = 6.6 Hz), 0.87 (3H, t, J = 7.4 Hz).

Example 19(57)

2'-(4-amidinophenylcarbamoyl)-4-((tetrahydropyran-4-ylmethyl)carbamoyl)-2-biphenylcarboxylic acid methanesulfonate

[0397]



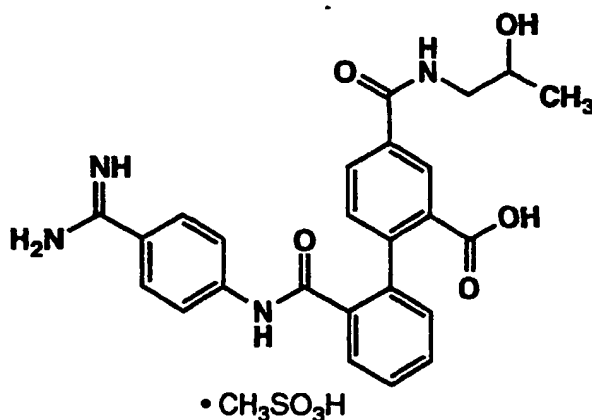
TLC : Rf 0.53 (Chloroform : Methanol : Water = 7 : 3 : 0.3) ;

NMR (d₆-DMSO) : δ 13.3-12.5 (1H, broad), 10.54 (1H, s), 9.19 (2H, s), 8.95 (2H, s), 8.69 (1H, brt, J = 6.0 Hz), 8.30 (1H, d, J = 2.0 Hz), 7.97 (1H, dd, J = 8.0 Hz, 2.0 Hz), 7.73 (4H, s), 7.70 (1H, dd, J = 7.5 Hz, 1.5 Hz), 7.62-7.47 (2H, m), 7.32 (1H, d, J = 8.0 Hz), 7.29-7.24 (1H, m), 3.83 (2H, dd, J = 11 Hz, 2.5 Hz), 3.25 (2H, brt, J = 11 Hz), 3.15 (2H, brt, J = 6.0 Hz), 2.34 (3H, s), 1.90-1.65 (1H, m), 1.58 (2H, brd, J = 13 Hz), 1.30-1.06 (2H, m).

Example 19(58)

2'-(4-amidinophenylcarbamoyl)-4-((2-hydroxypropyl)carbamoyl)-2-biphenylcarboxylic acid methanesulfonate

[0398]



EP 1 078 917 A1

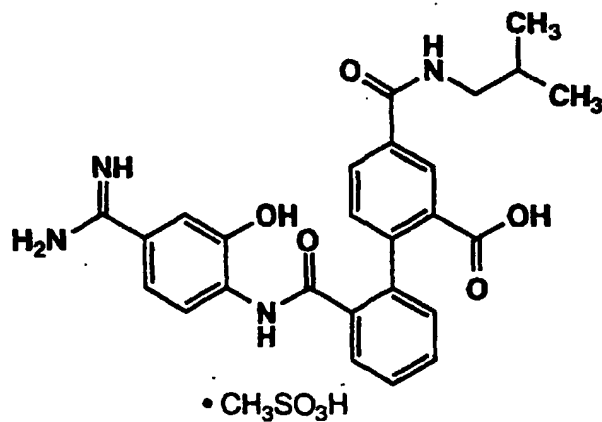
TLC : Rf 0.38 (Ethyl acetate : Acetic acid : Water = 3 : 1 : 1) ;

NMR (d_6 -DMSO) : δ 10.5 (1H, s), 9.17 (2H, br s), 8.87 (2H, br s), 8.61 (1H, t, J = 5.6 Hz), 8.32 (1H, d, J = 1.8 Hz), 7.99 (1H, dd, J = 1.8, 7.6 Hz), 7.73-7.68 (5H, m), 7.62-7.52 (2H, m), 7.35-7.26 (2H, m), 4.20-3.60 (1H, br s), 3.90-3.70 (1H, m), 3.22 (2H, d, J = 5.6 Hz), 2.36 (3H, s), 1.07 (3H, d, J = 6.2 Hz).

Example 19(59)

2'-(4-amidino-2-hydroxyphenylcarbamoyl)-4-((2-methylpropyl)carbamoyl)-2-biphenylcarboxylic acid methanesulfonate

[0399]



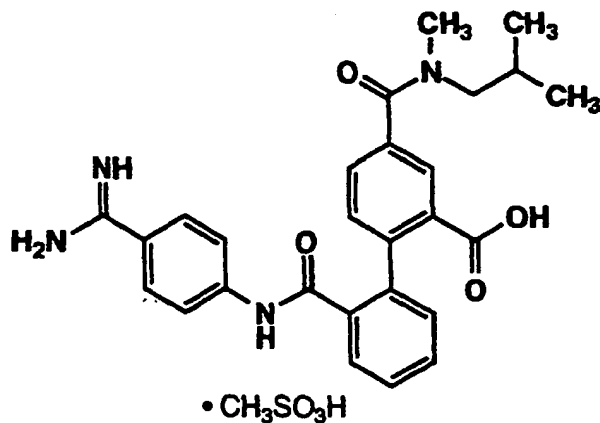
TLC : Rf 0.16 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d_6 -DMSO) : δ 13.6-13.0 (1H, broad), 10.56 (1H, s), 9.08 (2H, brs), 8.91 (1H, s), 8.81 (2H, brs), 8.67 (1H, brt, J = 5.5 Hz), 8.35 (1H, d, J = 2.0 Hz), 8.20 (1H, d, J = 8.5 Hz), 7.95 (1H, dd, J = 8.5 Hz, 2.0 Hz), 7.77-7.71 (1H, m), 7.58-7.48 (2H, m), 7.28 (1H, d, J = 8.5 Hz), 7.20-7.11 (2H, m), 7.08 (1H, d, J = 2.0 Hz), 3.06 (2H, brt, J = 6.0 Hz), 2.33 (3H, s), 1.93-1.73 (1H, m), 0.87 (6H, d, J = 6.5 Hz).

Example 19(60)

2'-(4-amidinophenylcarbamoyl)-4-(N-methyl-N-(2-methylpropyl)carbamoyl)-2-biphenylcarboxylic acid methanesulfonate

[0400]



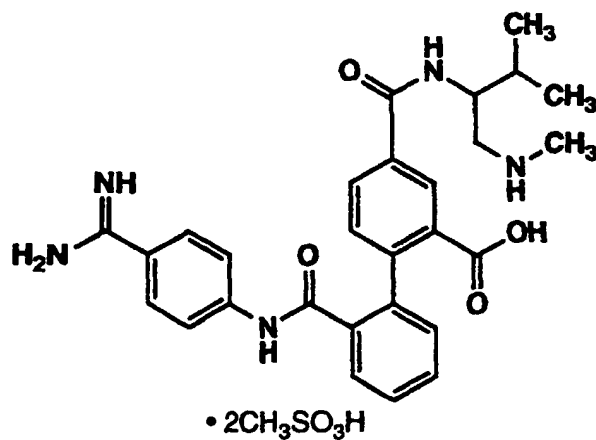
TLC : R_f 0.11 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d₆-DMSO) : δ 10.5 (1H, s), 9.17 (2H, br s), 8.91 (2H, br s), 7.73-7.40 (9H, m), 7.31 (2H, d, J = 7.8 Hz), 3.30-2.94 (2H, m, rotamers), 2.94 (3H, s, each of rotamers), 2.84 (3H, s, each of rotamers), 2.39 (3H, s, each of rotamers), 2.38 (3H, s, each of rotamers), 0.91 (6H, d, J = 6.6 Hz, each of rotamers), 0.62 (6H, m, each of rotamers).

Example 19(61)

2'-(4-amidinophenylcarbamoyl)-4-((2-methyl-1-(methylaminomethyl)propyl) carbamoyl)-2-biphenylcarboxylic acid dimethanesulfonate

[0401]



EP 1 078 917 A1

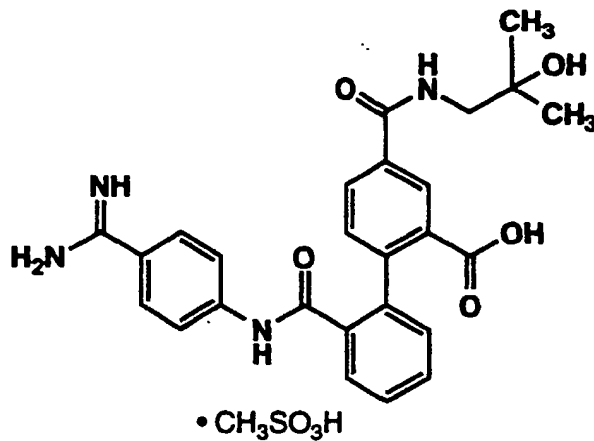
TLC : Rf 0.36 (Ethyl acetate : Acetic acid : Water = 3 : 1 : 1) ;

NMR (d₆-DMSO) : δ 13.0-12.0 (1H, br), 10.62 (1H, s), 9.18 (2H, br.s), 8.96 (2H, br.s), 8.49 (1H, d, J = 8.8 Hz), 8.6-8.3 (2H, br), 8.35 (1H, d, J = 1.4 Hz), 8.03 (1H, dd, J = 1.4, 8.0 Hz), 7.8-7.6 (1H, m), 7.75 (4H, like s), 7.55 (2H, m), 7.35 (1H, d, J = 8.0 Hz), 7.25 (1H, dd, J = 1.4, 6.8 Hz), 4.13 (1H, m), 3.3-2.9 (2H, br), 2.53 (3H, br.t, J = 5.0 Hz), 2.36 (6H, s), 1.83 (1H, m), 0.92 (3H, d, J = 6.4 Hz), 0.88 (3H, d, J = 6.4 Hz).

Example 19(62)

2'-(4-amidinophenylcarbamoyl)-4-((2-hydroxy-2-methylpropyl)carbamoyl)-2-biphenylcarboxylic acid methanesulfonate

[0402]



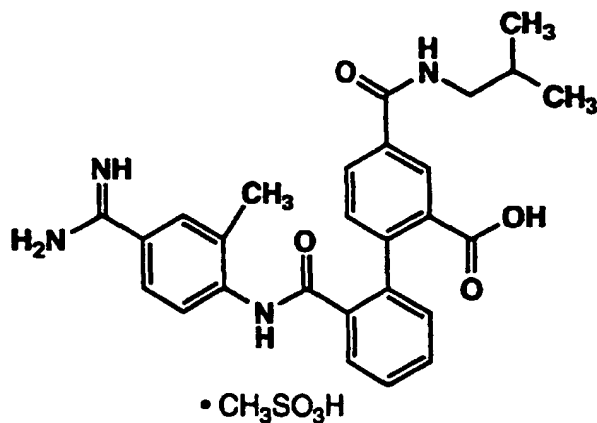
TLC : Rf 0.10 (Chloroform : Methanol : Water = 8 : 2 : 0.1) ;

NMR (d₆-DMSO) : δ 10.5 (1H, s), 9.16 (2H, br s), 8.85 (2H, br s), 8.47 (1H, t, J = 5.8 Hz), 8.32 (1H, d, J = 1.8 Hz), 8.01 (1H, dd, J = 1.8, 8.0 Hz), 7.74-7.69 (5H, m), 7.59-7.53 (2H, m), 7.35-7.26 (2H, m), 3.26 (2H, d, J = 5.8 Hz), 2.35 (3H, s), 1.11 (6H, s).

Example 19(63)

2'-(4-amidino-2-methylphenylcarbamoyl)-4-((2-methylpropyl)carbamoyl)-2-biphenylcarboxylic acid methanesulfonate

5 [0403]



25

TLC: R_f 0.28 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

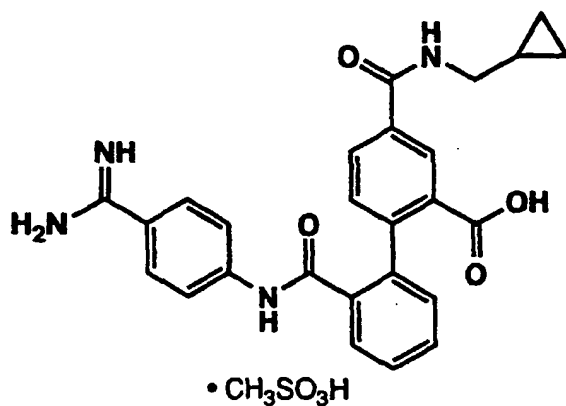
NMR (d₆-DMSO) : δ 13.5-12.6 (1H, broad), 9.49 (1H, s), 9.18 (2H, brs), 8.94-(2H, brs), 8.67 (1H, brt, J = 6.0 Hz), 8.30 (1H, d, J = 1.5 Hz), 7.99 (1H, dd, J = 8.0 Hz, 1.5 Hz), 7.75-7.70 (1H, m), 7.62-7.50 (5H, m), 7.36 (1H, d, J = 8.0 Hz), 7.27-7.22 (1H, m), 3.08 (2H, brt, J = 6.0 Hz), 2.32 (3H, s), 2.03 (3H, s), 1.96-1.74 (1H, m), 0.87 (6H, d, J = 7.0 Hz).

30

Example 19(64)

35 2'-(4-amidinophenylcarbamoyl)-4-((cyclopropylmethyl)carbamoyl)-2-biphenylcarboxylic acid methanesulfonate

[0404]



40

45

50

55

TLC : R_f 0.51 (Chloroform : Methanol : Water = 7 : 3 : 0.3) ;

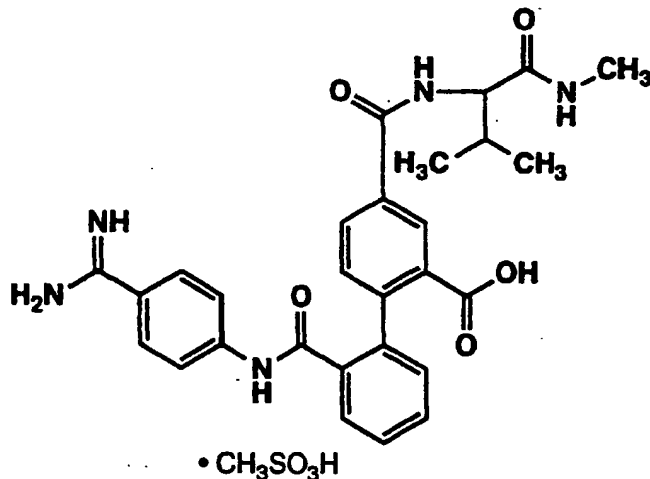
EP 1 078 917 A1

NMR (d_6 -DMSO) : δ 10.52 (1H, s), 9.16 (2H, s), 8.77 (2H, s), 8.76 (1H, br.t, J = 6.2 Hz), 8.32 (1H, d, J = 2.0 Hz), 7.98 (1H, dd, J = 2.0, 8.0 Hz), 7.73 (4H, s), 7.70 (1H, dd, J = 2.0, 8.0 Hz), 7.58 (1H, dt, J = 2.0, 8.0 Hz), 7.53 (1H, dt, J = 2.0, 8.0 Hz), 7.33 (1H, d, J = 8.0 Hz), 7.28 (1H, dd, J = 2.0, 8.0 Hz), 3.15 (2H, t, J = 6.2 Hz), 2.35 (3H, s), 1.04 (1H, m), 0.40-0.48 (2H, m), 0.19-0.27 (2H, m).

Example 19(65)

2'-(4-amidinophenylcarbamoyl)-4-((1-methylcarbamoyl-2-methylpropyl) carbamoyl)-2-biphenylcarboxylic acid methanesulfonate

[0405]



TLC : Rf 0.15 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d_6 -DMSO) : δ 9.07 (4H, br s), 8.37 (1H, d, J = 8.0 Hz), 8.06 (1H, s), 7.98 (1H, d, J = 4.6 Hz), 7.74-7.57 (6H, m), 7.48-7.44 (2H, m), 7.07-7.02 (1H, m), 6.98 (1H, d, J = 8.0 Hz), 4.15 (1H, t, J = 8.2 Hz), 2.56 (3H, d, J = 4.4 Hz), 2.32 (3H, s), 2.15-1.98 (1H, m), 0.88-0.83 (6H, m).

Example 19(66)

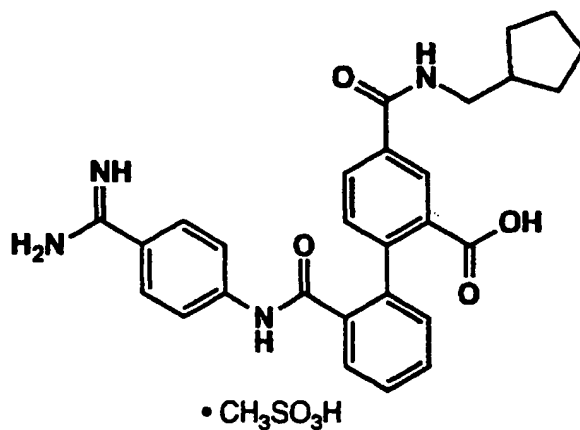
2'-(4-amidinophenylcarbamoyl)-4-((cyclopentylmethyl)carbamoyl)-2-biphenylcarboxylic acid methanesulfonate

5 [0406]

10

15

20



25

30

TLC : R_f 0.31 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d₆-DMSO) : δ 10.52 (1H, s), 9.16 (2H, s), 8.83 (2H, s), 8.66 (1H, br.d, J = 6.2 Hz), 8.30 (1H, d, J = 1.8 Hz), 7.97 (1H, dd, J = 1.8, 8.0 Hz), 7.73 (4H, s), 7.71 (1H, dd, J = 1.8, 8.0 Hz), 7.53-7.58 (2H, m), 7.32 (1H, d, J = 8.0 Hz), 7.27 (1H, dd, J = 1.8, 8.0 Hz), 3.19 (2H, t, J = 6.2 Hz), 2.35 (3H, s), 2.16 (1H, m), 1.53-1.69 (6H, m), 1.22-1.24 (2H, m).

Example 19(67)

2'-(4-amidinophenylcarbamoyl)-4-((cyclobutylmethyl)carbamoyl)-2-biphenylcarboxylic acid methanesulfonate

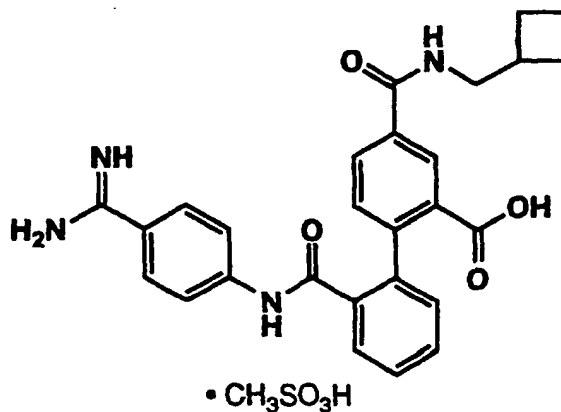
35

[0407]

40

45

50



55

TLC : R_f 0.27 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d₆-DMSO) : δ 10.53 (1H, s), 9.17 (2H, s), 8.87 (2H, s), 8.64 (1H, br.d, J = 6.6 Hz), 8.30 (1H, d, J = 1.8 Hz),

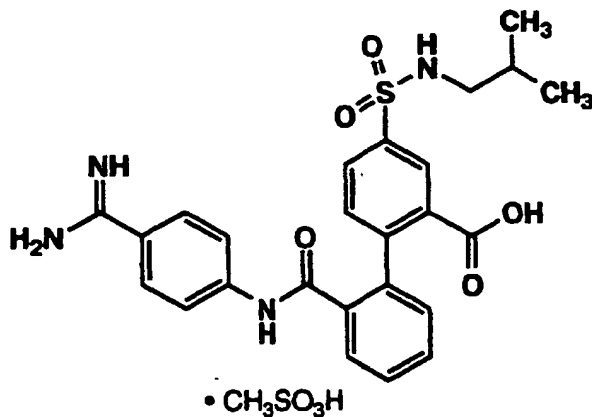
EP 1 078 917 A1

7.96 (1H, dd, J = 1.8, 8.0 Hz), 7.74 (4H, s), 7.71 (1H, dd, J = 1.8, 8.0 Hz), 7.53-7.58 (2H, m), 7.32 (1H, d, J = 8.0 Hz), 7.27 (1H, dd, J = 1.8, 8.0 Hz), 3.30 (2H, t, J = 6.6 Hz), 2.58 (1H, m), 2.35 (3H, s), 1.66-2.00 (6H, m).

Example 19(68)

2'-(4-amidinophenylcarbamoyl)-4-((2-methylpropyl)sulfamoyl)-2-biphenylcarboxylic acid methanesulfonate

[0408]



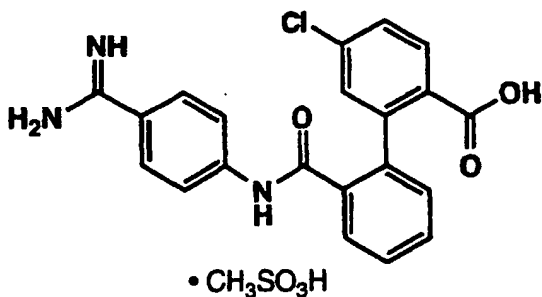
TLC : Rf 0.38 (Chloroform : Methanol : Water = 8 : 2 : 0.1) ;

NMR (d₆-DMSO) : δ 10.6 (1H, br s), 9.14 (2H, br s), 8.79 (2H, br s), 8.20 (1H, d, J = 1.8 Hz), 7.89 (1H, dd, J = 1.8, 8.2 Hz), 7.80-7.62 (5H, m), 7.62-7.50 (2H, m), 7.45 (1H, d, J = 8.2 Hz), 7.33-7.29 (1H, m), 2.60-2.40 (2H, m), 2.30 (3H, s), 1.70-1.50 (1H, m), 0.78 (6H, d, J = 6.6 Hz).

Example 19(69)

2'-(4-amidinophenylcarbamoyl)-5-chloro-2-biphenylcarboxylic acid methanesulfonate

[0409]



TLC : Rf 0.25 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

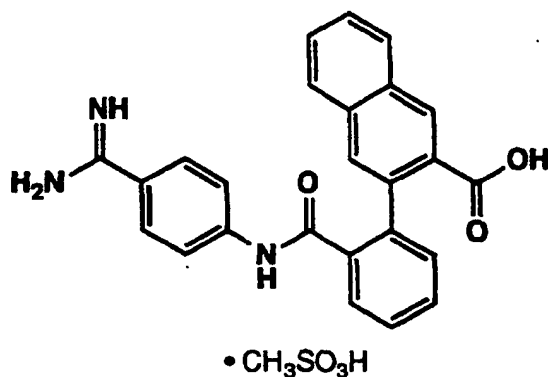
NMR (d₆-DMSO) : δ 13.2-12.4 (1H, broad), 10.50 (1H, s), 9.14 (2H, s), 8.87 (2H, s), 7.90-7.40 (9H, m), 7.40-7.26

(2H, m), 2.35 (3H, s).

Example 19(70)

5 3-(2-(4-amidinophenylcarbamoyl)phenyl)-2-naphthalenecarboxylic acid methanesulfonate

[0410]



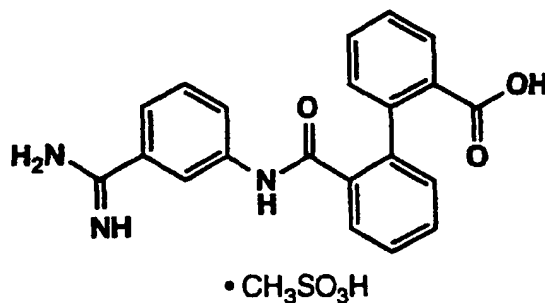
TLC : R_f 0.52 (Ethyl acetate : Acetic acid : Water = 3 : 1 : 0.5) ;

NMR (d₆-DMSO) : δ 10.44 (1H, s), 9.09 (2H, br.s), 8.78 (2H, br.s), 8.46 (1H, s), 8.07 (1H, d, J = 8.0 Hz), 7.92 (1H, d, J = 8.0 Hz), 7.76 (1H, s), 7.8-7.5 (9H, m), 7.36 (1H, d, J = 8.0 Hz), 4.31 (1H, br), 2.35 (3H, s).

Example 19(71)

2'-(3-amidinophenylcarbamoyl)-2-biphenylcarboxylic acid methanesulfonate

[0411]



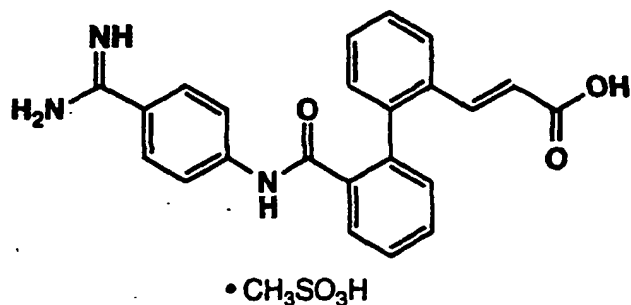
TLC : R_f 0.50 (Chloroform : Methanol : Water = 7 : 3 : 0.3) ;

NMR (d₆-DMSO) : δ 10.37 (1H, s), 9.27 (2H, s), 8.93 (2H, s), 8.05 (1H, s), 7.83 (1H, d, J = 7.8 Hz), 7.63-7.67 (2H, m), 7.48-7.54 (4H, m), 7.37-7.46 (2H, m), 7.22-7.25 (2H, m), 2.35 (3H, s).

Example 19(72)

2-(2-(4-amidinophenylcarbamoyl)phenyl)cinnamic acid methanesulfonate

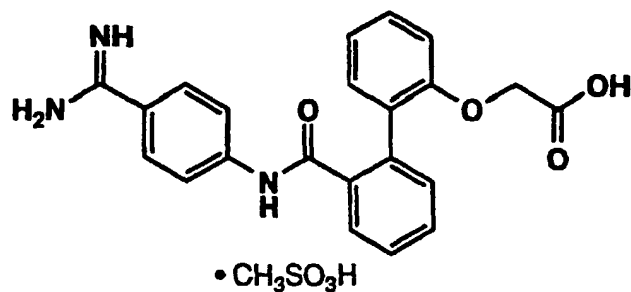
[0412]

TLC : R_f 0.17 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;NMR (d₆-DMSO) : δ 12.6-12.0 (1H, broad), 10.68 (1H, s), 9.14 (2H, brs), 8.86 (2H, brs), 7.85-7.59 (8H, m), 7.45-7.24 (5H, m), 6.38 (1H, d, J = 16 Hz), 2.34 (3H, s).

Example 19(73)

2'-(4-amidinophenylcarbamoyl)biphenyl-2-yloxyacetic acid methanesulfonate

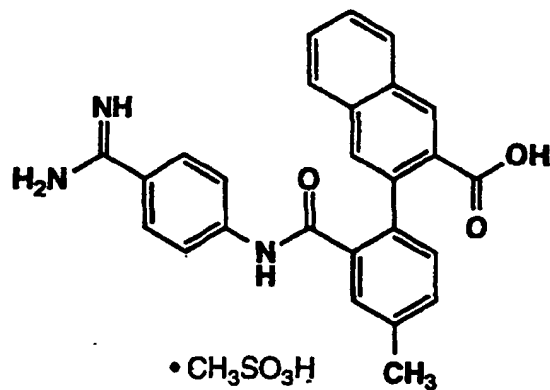
[0413]

TLC : R_f 0.10 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;NMR (d₆-DMSO) : δ 13.3-12.6 (1H, broad), 10.42 (1H, s), 9.15 (2H, brs), 8.87 (2H, brs), 7.75 (4H, s), 7.65-7.44 (4H, m), 7.28-7.21 (2H, m), 6.98 (1H, t, J = 8.0 Hz), 6.84 (1H, d, J = 8.0 Hz), 4.45 (2H, s), 2.35 (3H, s).

Example 19(74)

3-(2-(4-amidinophenylcarbamoyl)-4-methylphenyl)-2-naphthalenecarboxylic acid methanesulfonate

5 [0414]

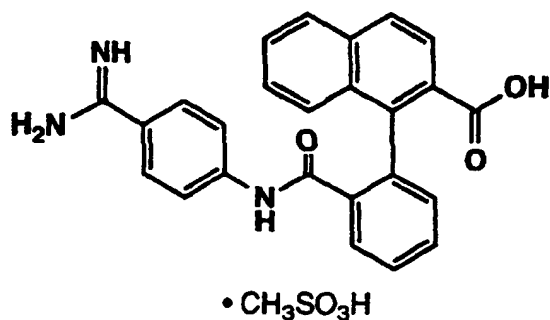


25 TLC : R_f 0.17 (Chloroform : Methanol : Acetic acid = 4 : 1 : 0.1) ;
 NMR (d₆-DMSO) : δ 13.0-12.6 (1H, br), 10.44 (1H, s), 9.09 (2H, s), 8.74 (2H, s), 8.45 (1H, s), 8.06 (1H, d, J = 6.4 Hz), 7.92 (1H, d, J = 8.8 Hz), 7.8-7.5 (5H, m), 7.73 (1H, s), 7.66 (2H, s), 7.40 (1H, d, J = 8.4 Hz), 7.25 (1H, d, J = 8.0 Hz), 2.46 (3H, s), 2.33 (3H, s).

30 Example 19(75)

1-(2-(4-amidinophenylcarbamoyl)phenyl)-2-naphthalenecarboxylic acid methanesulfonate

35 [0415]



50

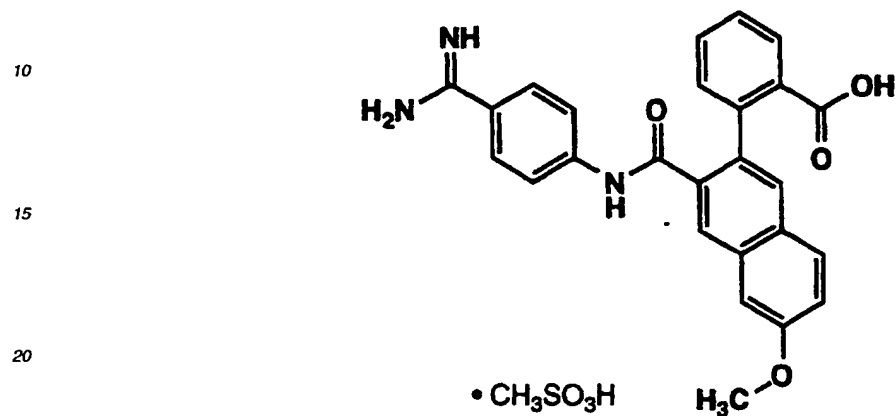
55 TLC : R_f 0.14 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;
 NMR (d₆-DMSO) : δ 13.3-12.7 (1H, broad), 10.50 (1H, s), 9.09 (2H, brs), 8.81 (2H, brs), 7.99-7.95 (2H, m), 7.91-7.81 (2H, m), 7.67-7.51 (7H, m), 7.42 (1H, t, J = 8.0 Hz), 7.26-7.20 (2H, m), 2.33 (3H, s).

55

Example 19(76)

2-(3-(4-amidinophenylcarbamoyl)-6-methoxynaphthalen-2-yl)benzoic acid methanesulfonate

5 [0416]



25

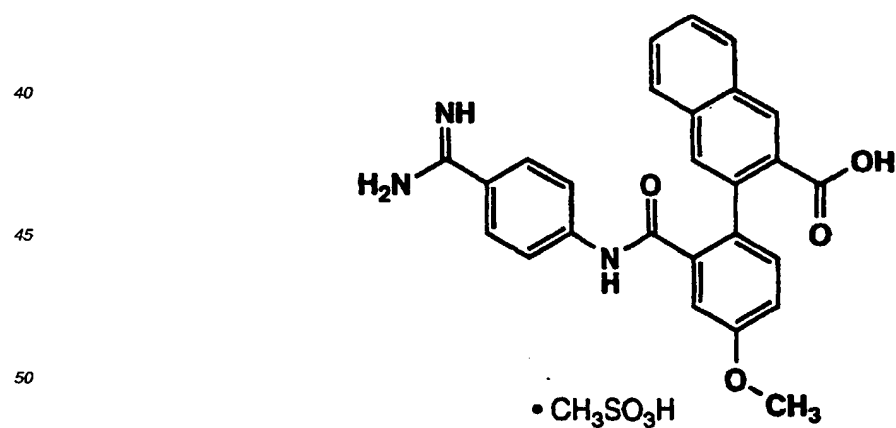
TLC : R_f 0.38 (Chloroform : Methanol : Water = 10 : 3 : 0.2) ;NMR (d₆-DMSO) : δ 12.62 (1H, br.s), 10.58 (1H, br.s), 9.14 (2H, br.s), 8.78 (2H, br.s), 8.15 (1H, s), 7.91 (1H, d, J = 9.2 Hz), 7.84 (1H, d, J = 7.8 Hz), 7.74 (4H, like s), 7.71 (1H, s), 7.6-7.2 (5H, m), 3.91 (3H, s), 2.31 (3H, s).

30

Example 19(77)

3-(2-(4-amidinophenylcarbamoyl)-4-methoxyphenyl)-2-naphthalenecarboxylic acid methanesulfonate

35 [0417]



55

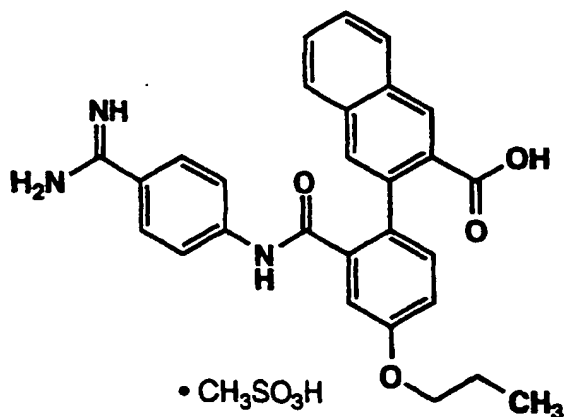
TLC : R_f 0.20 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;NMR (d₆-DMSO) : δ 12.8 (1H, brs), 10.46 (1H, s), 9.10 (2H, brs), 8.82 (2H, brs), 8.43 (1H, s), 8.08-8.03 (1H, m),

7.94-7.88 (1H, m), 7.74-7.52 (7H, m), 7.28 (1H, d, J = 8.0 Hz), 7.24 (1H, d, J = 3.0 Hz), 7.15 (1H, dd, J = 8.0 Hz, 3.0 Hz), 3.89 (3H, s), 2.33 (3H, s).

Example 19(78)

3-(2-(4-amidinophenylcarbamoyl)-4-propoxyphenyl)-2-naphthalenecarboxylic acid methanesulfonate

[0418]



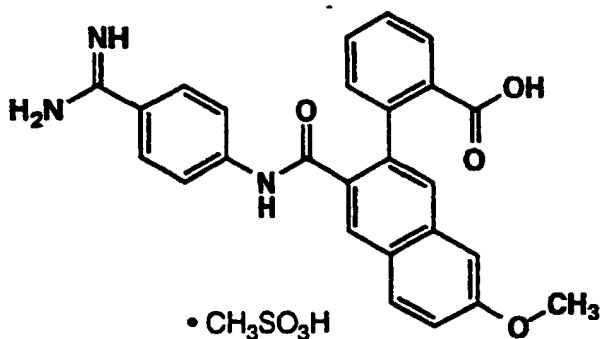
TLC : R_f 0.18 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d₆-DMSO) : δ 12.8 (1H, brs), 10.45 (1H, s), 9.10 (2H, brs), 8.83 (2H, brs), 8.43 (1H, s), 8.08-8.02 (1H, m), 7.94-7.89 (1H, m), 7.73 (1H, s), 7.67 (4H, s), 7.62-7.56 (2H, m), 7.26 (1H, d, J = 8.0 Hz), 7.23 (1H, d, J = 2.5 Hz), 7.14 (1H, dd, J = 8.0 Hz, 2.5 Hz), 4.06 (2H, t, J = 7.0 Hz), 2.34 (3H, s), 1.79 (2H, sextet, J = 7.0 Hz), 1.03 (3H, t, J = 7.0 Hz).

Example 19(79)

2-(3-(4-amidinophenylcarbamoyl)-7-methoxynaphthalen-2-yl)benzoic acid methanesulfonate

[0419]



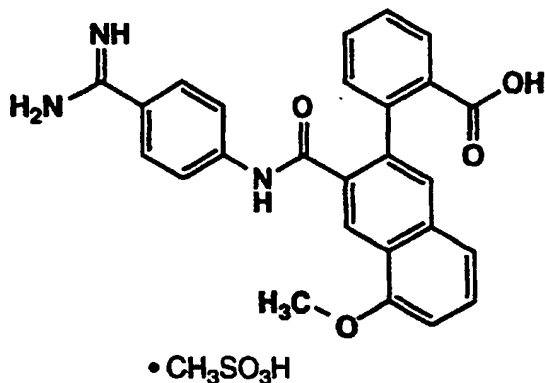
TLC : Rf 0.23 (Chloroform : Methanol : Water = 10 : 3 : 0.2) ;

NMR (d₆-DMSO) : δ 12.6-11.9 (1H, br), 10.57 (1H, s), 9.15 (2H, br.s), 8.82 (2H, br.s), 8.20 (1H, s), 8.00 (1H, d, J = 8.8 Hz), 7.85 (1H, d, J = 7.4 Hz), 7.9-7.6 (5H, m), 7.55 (1H, m), 7.5-7.3 (2H, m), 7.4-7.1 (2H, m), 3.89 (3H, m), 2.33 (3H, s).

Example 19(80)

2-(3-(4-amidinophenylcarbamoyl)-5-methoxynaphthalen-2-yl)benzoic acid methanesulfonate

[0420]



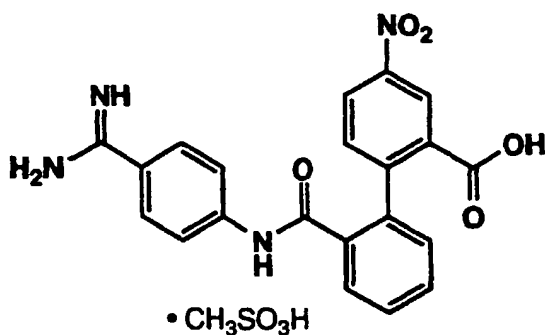
TLC : Rf 0.41 (Chloroform : Methanol : Water = 10 : 3 : 0.2) ;

NMR (d₆-DMSO) : δ 12.70 (1H, br), 10.66 (1H, s), 9.16 (2H, br.s), 8.87 (2H, br.s), 8.44 (1H, s), 7.86 (1H, dd, J = 1.4, 7.8 Hz), 7.75 (4H, s), 7.6-7.5 (4H, m), 7.43 (1H, dt, J = 1.4, 7.8 Hz), 7.32 (1H, dd, J = 1.4, 7.8 Hz), 7.09 (1H, m), 4.04 (3H, s), 2.34 (3H, s).

Example 19(81)

2'-(4-amidinophenylcarbamoyl)-4-nitro-2-biphenylcarboxylic acid methanesulfonate

[0421]



EP 1 078 917 A1

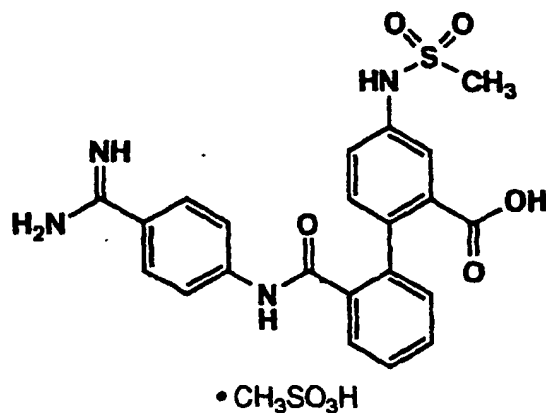
TLC : Rf 0.13 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d_6 -DMSO) : δ 13.5-12.8 (1H, broad), 10.68 (1H, s), 9.15 (2H, brs), 8.87 (2H, brs), 8.56 (1H, d, J = 2.5 Hz), 8.37 (1H, dd, J = 8.0 Hz, 2.5 Hz), 7.81-7.70 (5H, m), 7.66-7.54 (2H, m), 7.53 (1H, d, J = 8.0 Hz), 7.34-7.29 (1H, m), 2.35 (3H, s).

Example 19(82)

2'-(4-amidinophenylcarbonyl)-4-methylsulfonylamino-2-biphenylcarboxylic acid methanesulfonate

[0422]



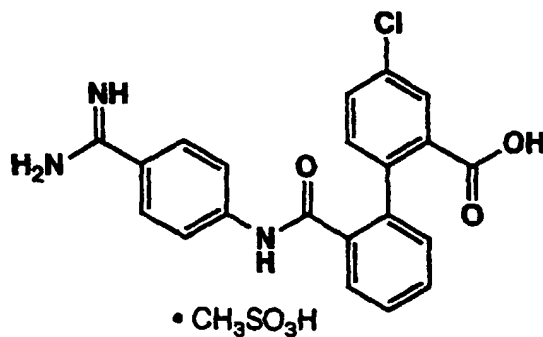
TLC : Rf 0.33 (Chloroform : Methanol : Water = 7 : 3 : 0.3) ;

NMR (d_6 -DMSO) : δ 10.40 (1H, s), 9.98 (1H, s), 9.14 (2H, brs), 8.89 (2H, brs), 7.74 (2H, d, J = 9.0 Hz), 7.67 (2H, d, J = 9.0 Hz), 7.66-7.60 (2H, m), 7.58-7.43 (2H, m), 7.32 (1H, dd, J = 8.0 Hz, 2.0 Hz), 7.23 (1H, dd, J = 8.0 Hz, 2.0 Hz), 7.20 (1H, d, J = 8.0 Hz), 2.96 (3H, s), 2.34 (3H, s).

Example 19(83)

2'-(4-amidinophenylcarbonyl)-4-chloro-2-biphenylcarboxylic acid methanesulfonate

[0423]



EP 1 078 917 A1

TLC : Rf 0.49 (Chloroform : Methanol : Water = 7 : 3 : 0.3) ;

NMR (d_6 -DMSO) : δ 10.52 (1H, s), 9.15 (2H, s), 8.86 (2H, s), 7.81 (1H, d, J = 2.0 Hz), 7.74 (4H, s), 7.69 (1H, dd, J = 2.0, 7.6 Hz), 7.53-7.62 (3H, m), 7.27 (1H, dd, J = 2.0, 7.6 Hz), 7.26 (1H, d, J = 7.6 Hz), 2.33 (3H, s).

5 Example 19(84)

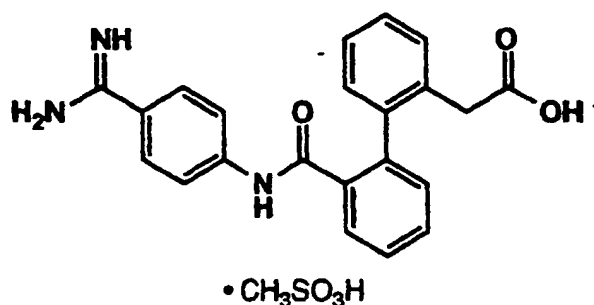
2'-(4-amidinophenylcarbamoyl)biphenyl-2-ylacetic acid methanesulfonate

[0424]

10

15

20



25

TLC : Rf 0.33 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d_6 -DMSO) : δ 12.7-12.4 (1H, broad), 10.26 (1H, s), 9.14 (2H, brs), 8.91 (2H, brs), 7.72-7.65 (3H, m), 7.60-7.48 (4H, m), 7.39-7.32 (2H, m), 7.29-7.08 (3H, m), 3.77 (1H, d, J = 17 Hz), 3.55 (1H, d, J = 17 Hz), 2.33 (3H, s).

30

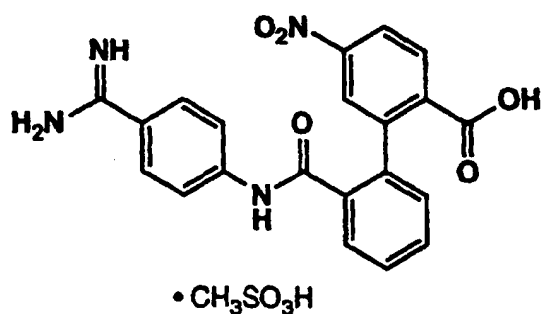
Example 19(85)

2'-(4-amidinophenylcarbamoyl)-5-nitro-2-biphenylcarboxylic acid methanesulfonate

35 [0425]

40

45



50

TLC : Rf 0.24 (Chloroform : Methanol : Water = 8 : 2 : 0.1) ;

NMR (d_6 -DMSO) : δ 10.6 (1H, s), 9.15 (2H, brs), 8.84 (2H, brs), 8.26 (1H, dd, J = 2.6, 8.4 Hz), 8.07-8.02 (2H, m), 7.85-7.58 (7H, m), 7.38 (1H, dd, J = 2.2, 7.8 Hz), 2.39 (3H, s).

55

Example 19(86)

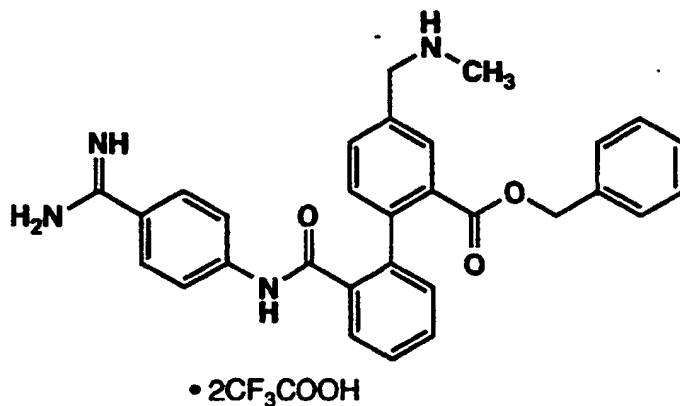
Benzyl 2'-(4-amidinophenylcarbamoyl)-4-methylaminomethyl-2-biphenylcarboxylic acid ditrifluoroacetate

5 [0426]

10

15

20



25

TLC : Rf 0.57 (Chloroform : Methanol : Water = 7 : 3 : 0.3) ;

NMR (CD₃OD) : δ 8.02 (1H, d, J = 1.6 Hz), 7.64-7.70 (6H, m), 7.54 (1H, dt, J = 1.6, 7.6 Hz), 7.50 (1H, dt, J = 1.6, 7.6 Hz), 7.42 (1H, d, J = 8.0 Hz), 7.23-7.28 (4H, m), 7.10-7.15 (2H, m), 5.11 (2H, s), 4.23 (2H, s), 2.70 (3H, s).

30 Example 19(87)

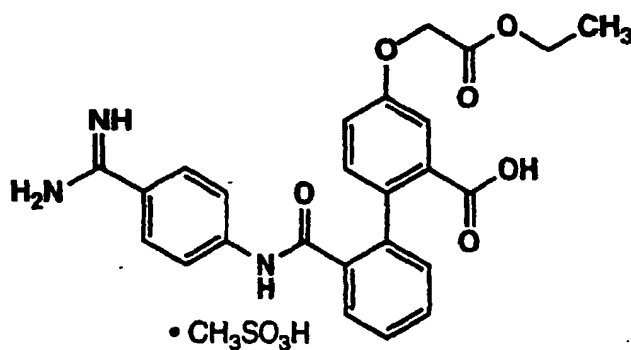
2'-(4-amidinophenylcarbamoyl)-4-ethoxycarbonylmethoxy-2-biphenyl carboxylic acid methanesulfonate

35 [0427]

40

45

50



55

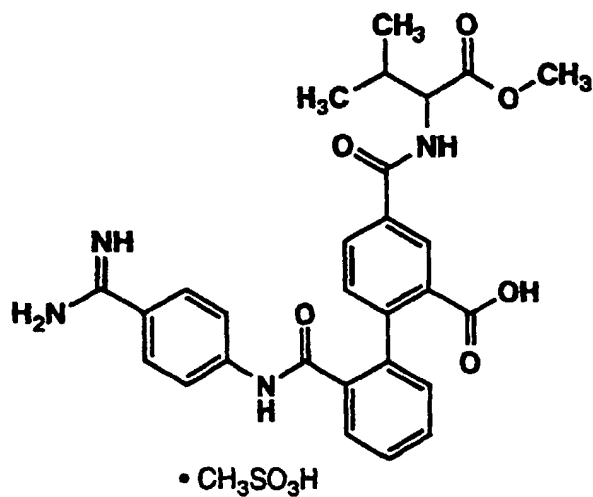
TLC : Rf 0.31 (Chloroform : Methanol : Water = 10 : 3 : 0.2) ;

NMR (d₆-DMSO) : δ 13.4-12.4 (1H, br), 10.67 (1H, br.s), 9.21 (2H, br.s), 9.05 (2H, br.s), 7.8-7.5 (5H, m), 7.6-7.4 (2H, m), 7.3-7.0 (4H, m), 4.82 (2H, s), 4.14 (2H, q, J = 7.4 Hz), 2.34 (3H, s), 1.17 (3H, t, J = 7.4 Hz).

Example 19(88)

2'-(4-amidinophenylcarbamoyl)-4-((1-methoxycarbonyl-2-methylpropyl) carbamoyl)-2-biphenylcarboxylic acid methanesulfonate

[0428]



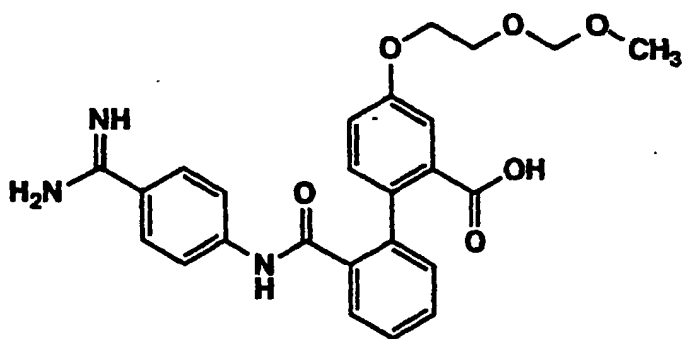
TLC : R_f 0.51 (Chloroform : Methanol : Water = 7 : 3 : 0.3);

NMR (CD₃OD): δ 9.04 (2H, br.s), 8.61 (2H, br.s), 8.34 (1H, d, J = 1.6 Hz), 7.96 (1H, dd, J = 1.6, 7.8 Hz), 7.64-7.74 (5H, m), 7.53-7.59 (2H, m), 7.38 (1H, d, J = 7.8-Hz), 7.26 (1H, dd, J = 1.6, 7.8 Hz), 4.47 (1H, d, J = 6.6 Hz), 3.75 (3H, s), 2.71 (3H, s), 2.26 (1H, septet, J = 6.6 Hz), 1.02 (3H, d, J = 6.6 Hz), 1.00 (3H, d, J = 6.6 Hz).

Example 19(89)

2'-(4-amidinophenylcarbamoyl)-4-(2-(methoxymethoxy)ethoxy)-biphenylcarboxylic acid

[0429]



EP 1 078 917 A1

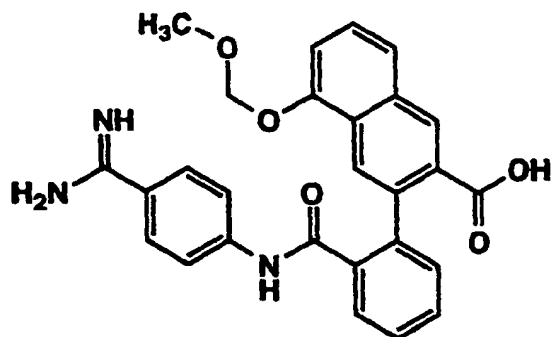
TLC : Rf 0.54 (Chloroform : Methanol : Water = 10 : 3 : 0.2) ;

NMR (d_6 -DMSO) : δ 13.0-12.0 (1H, br), 10.52 (1H, br.s), 9.3-9.0 (3H, br), 7.76 (2H, d, J = 8.8 Hz), 7.67 (2H, d, J = 8.8 Hz), 7.7-7.5 (1H, m), 7.6-7.4 (2H, m), 7.30 (1H, d, J = 2.6 Hz), 7.3-7.0 (3H, m), 4.60 (2H, s), 4.14 (2H, t, J = 4.4 Hz), 3.76 (2H, t, J = 4.4 Hz), 3.25 (3H, s).

Example 19(90)

3-(2-(4-amidinophenylcarbamoyl)phenyl)-5-methoxymethoxy-2-naphthalenecarboxylic acid

[0430]



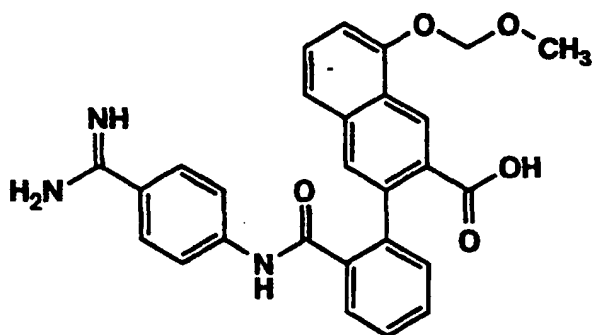
TLC : Rf 0.50 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d_6 -DMSO) : δ 10.80 (1H, br.s), 9.2-8.9 (3H, br), 8.39 (1H, s), 8.39 (1H, s), 7.95 (1H, s), 7.8-7.6 (6H, m), 7.6-7.4 (3H, m), 7.34 (1H, m), 7.18 (1H, d, J = 8.0 Hz), 5.35 (2H, s), 3.30 (3H, s).

Example 19(91)

3-(2-(4-amidinophenylcarbamoyl)phenyl)-8-methoxymethoxy-2-naphthalenecarboxylic acid

[0431]



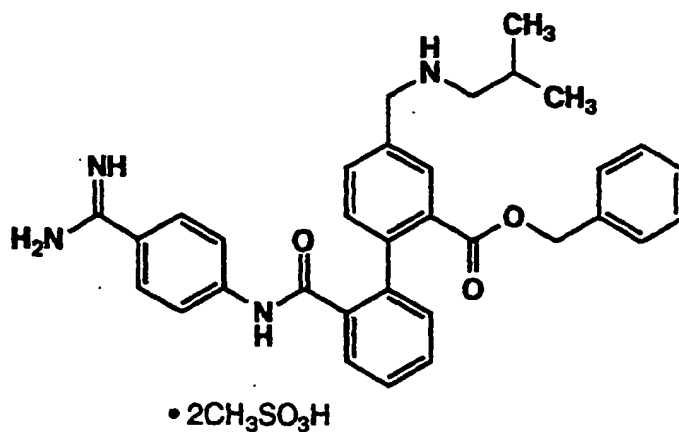
TLC : Rf 0.62 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d_6 -DMSO) : δ 10.69 (1H, br.s), 9.2-9.0 (3H, br), 8.69 (1H, s), 7.8-7.6 (6H, m), 7.6-7.4 (4H, m), 7.33 (1H, dd, J = 2.2, 7.4 Hz), 7.15 (1H, dd, J = 3.0, 5.4 Hz), 5.45 (2H, s), 3.46 (3H, s).

Example 19(92)

Benzyl 2'-(4-amidinophenylcarbamoyl)-4-((2-methylpropyl)aminomethyl)-2-biphenylcarboxylic acid dimethanesulfonate

[0432]

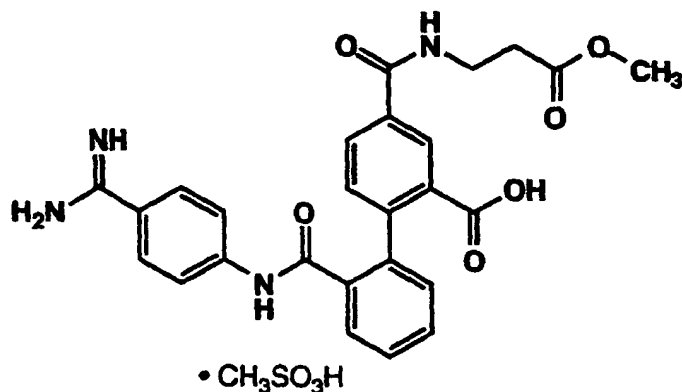


TLC : Rf 0.37 (Chloroform : Methanol : Water = 8 : 2 : 0.1).

Example 19(93)

2'-(4-amidinophenylcarbamoyl)-4-((2-methoxycarbonyl)ethyl)carbamoyl)-2-biphenylcarboxylic acid methanesulfonate

[0433]



TLC : Rf 0.43 (Chloroform : Methanol : Water = 7 : 3 : 0.3) ;

NMR (d₆-DMSO) : δ 13.1-12.7 (1H, broad), 10.54 (1H, s), 9.15 (2H, brs), 8.88 (2H, brs), 8.75 (1H, brt, J = 5.5 Hz), 8.28 (1H, d, J = 2.0 Hz), 7.94 (1H, dd, J = 8.0 Hz, 2.0 Hz), 7.72 (4H, s), 7.69 (1H, dd, J = 7.5 Hz, 1.5 Hz), 7.62-7.47 (2H, m), 7.32 (1H, d, J = 8.0 Hz), 7.27 (1H, dd, J = 7.5 Hz, 1.5 Hz), 3.59 (3H, s), 3.49 (2H, q, J = 7.0 Hz), 2.59 (2H, t, J = 7.0 Hz), 2.34 (3H, s).

Example 19(94)

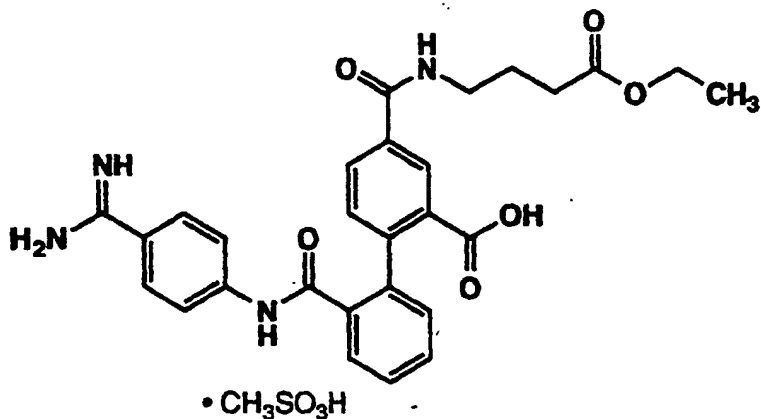
2'-{(4-amidinophenylcarbamoyl)-4-((3-ethoxycarbonylpropyl)carbamoyl)-2-biphenylcarboxylic acid methanesulfonate

5 [0434]

10

15

20



25

30

TLC : R_f 0.55 (Chloroform : Methanol : Water = 7 : 3 : 0.3) ;

NMR (d₆-DMSO) : δ 13.1-12.6 (1H, broad), 10.54 (1H, s), 9.16 (2H, brs), 8.91 (2H, brs), 8.68 (1H, brt, J = 5.5 Hz), 8.29 (1H, d, J = 2.0 Hz), 7.96 (1H, dd, J = 8.0 Hz, 2.0 Hz), 7.73 (4H, s), 7.70 (1H, dd, J = 7.5 Hz, 1.5 Hz), 7.62-7.47 (2H, m), 7.32 (1H, d, J = 8.0 Hz), 7.27 (1H, dd, J = 7.5 Hz, 1.5 Hz), 4.03 (2H, q, J = 7.0 Hz), 3.33-3.22 (2H, m), 2.34 (3H, s), 2.34 (2H, t, J = 7.0 Hz), 1.77 (2H, quint, J = 7.0 Hz), 1.15 (3H, t, J = 7.0 Hz).

Example 19(95)

35 2'-{(4-amidinophenylcarbamoyl)-4-((1-*t*-butoxycarbonylpiperidin-4-ylmethyl) carbamoyl)-2-biphenylcarboxylic acid

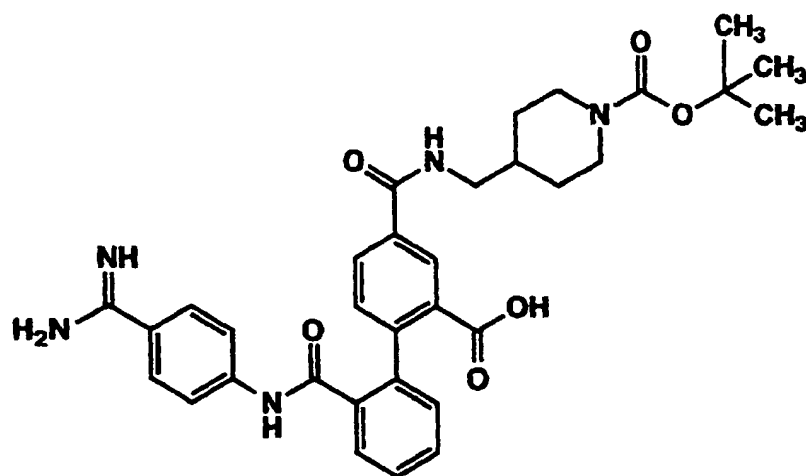
[0435]

40

45

50

55



EP 1 078 917 A1

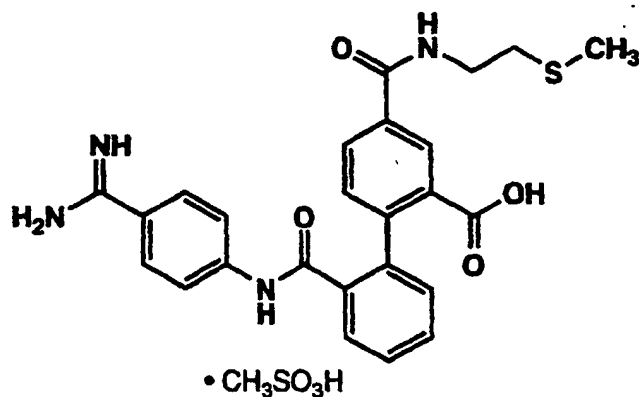
TLC : Rf 0.49 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d_6 -DMSO) : δ 10.9 (1H, br s), 9.19 (2H, br s), 8.97 (2H, br s), 8.70 (1H, t, J = 6.2 Hz), 8.27 (1H, d, J = 1.8 Hz), 7.94 (1H, dd, J = 1.8, 8.0 Hz), 7.80-7.60 (5H, m), 7.60-7.50 (2H, m), 7.30-7.23 (2H, m), 3.93 (2H, br d, J = 12.0 Hz), 3.16 (2H, br s), 2.80-2.50 (2H, m), 1.80-1.60 (3H, m), 1.39 (9H, s), 1.10-0.99 (2H, m).

Example 19(96)

2'-(4-amidinophenylcarbamoyl)-4-((2-methylthioethyl)carbamoyl)-2-biphenylcarboxylic acid methanesulfonate

[0436]



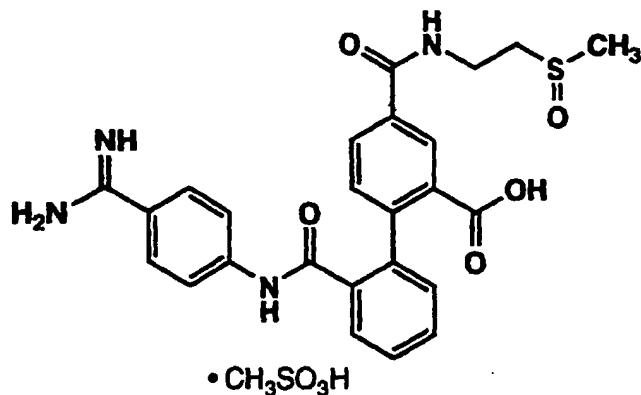
TLC : Rf 0.58 (Chloroform : Methanol : Water = 10 : 3 : 0.2) ;

NMR (d_6 -DMSO) : δ 13.0-12.0 (1H, br), 10.52 (1H, s), 9.14 (2H, br.s), 8.83 (2H, br.s), 8.79 (1H, br.t), 8.29 (1H, s), 7.96 (1H, d, J = 8.0 Hz), 7.72 (4H, like s), 7.8-7.6 (1H, m), 7.6-7.5 (2H, m), 7.33 (1H, d, J = 8.0 Hz), 7.4-7.2 (1H, m), 3.45 (2H, br.q), 2.64 (2H, t, J = 6.8 Hz), 2.34 (3H, s), 2.08 (3H, s).

Example 19(97)

2'-(4-amidinophenylcarbamoyl)-4-((2-methylsulfinylethyl)carbamoyl)-2-biphenylcarboxylic acid methanesulfonate

[0437]



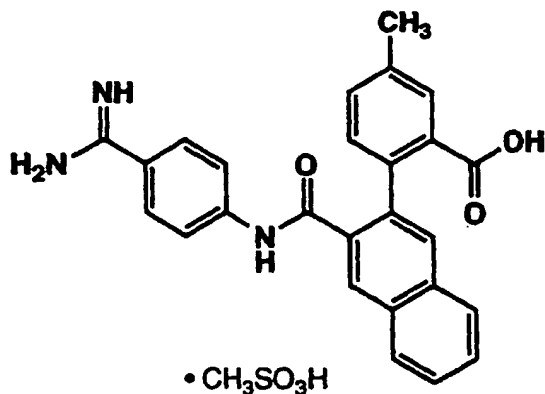
TLC : Rf 0.24 (Chloroform : Methanol : Water = 10 : 3 : 0.2) ;

NMR (d_6 -DMSO) : δ 10.52 (1H, s), 9.14 (2H, s), 8.96 (1H, br.t, J = 1.4 Hz), 8.88 (2H, s), 8.30 (1H, s), 7.96 (1H, d, J = 8.2 Hz), 7.72 (4H, like s), 7.8-7.6 (1H, m), 7.6-7.5 (2H, m), 7.34 (1H, d, J = 8.2 Hz), 7.28 (1H, d, J = 8.2 Hz), 6.0-4.6 (1H, br), 3.8-3.5 (2H, br), 3.06 (1H, dt, J = 13.8, 6.4 Hz), 2.88 (1H, dt, J = 13.8, 6.8 Hz), 2.58 (3H, s), 2.38 (3H, s).

Example 19(98)

2-(3-(4-amidinophenylcarbamoyl)naphthalen-2-yl)-5-methylbenzoic acid methanesulfonate

[0438]



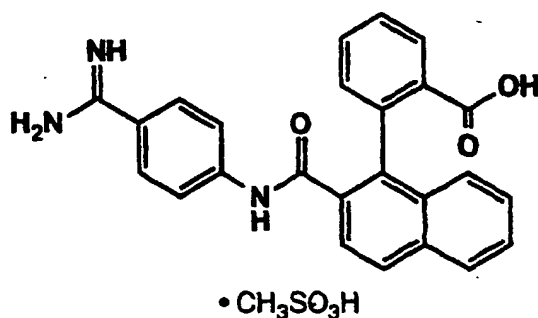
TLC : Rf 0.27 (Chloroform : Methanol : Acetic acid = 4 : 1 : 0.1) ;

NMR (d_6 -DMSO) : δ 12.6 (1H, brs), 10.7 (1H, s), 9.17 (2H, s), 8.83 (2H, s), 8.25 (1H, s), 8.15-8.05 (1H, m), 8.05-7.95 (1H, m), 7.77 (5H, s), 7.7-7.6 (3H, m), 7.37 (1H, dt, J = 8.2, 1.0 Hz), 7.22 (1H, d, J = 7.8 Hz), 2.37 (3H, s), 2.33 (3H, s).

Example 19(99)

2-(2-(4-amidinophenylcarbamoyl)naphthalen-1-yl)benzoic acid methanesulfonate

[0439]



EP 1 078 917 A1

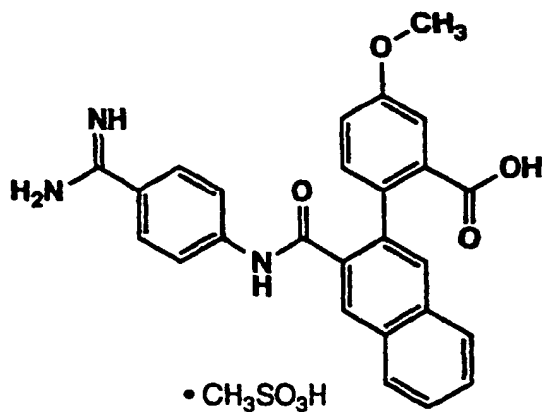
TLC : Rf 0.20 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d_6 -DMSO) : δ 13.0-12.5 (1H, broad), 10.40 (1H, s), 9.15 (2H, brs), 8.87 (2H, brs), 8.07 (1H, d, J = 8.0 Hz), 8.05 (1H, d, J = 8.0 Hz), 7.96 (1H, dd, J = 7.5 Hz, 1.5 Hz), 7.73 (1H, d, J = 8.0 Hz), 7.72 (2H, d, J = 9.0 Hz), 7.62 (2H, d, J = 9.2), 7.58-7.42 (4H, m), 7.27 (1H, dd, J = 7.5 Hz, 1.5 Hz), 7.21 (1H, d, J = 8.0 Hz), 2.33 (3H, s).

Example 19(100)

2-(3-(4-amidinophenylcarbamoyl)naphthalen-2-yl)-5-methoxybenzoic acid methanesulfonate

[0440]



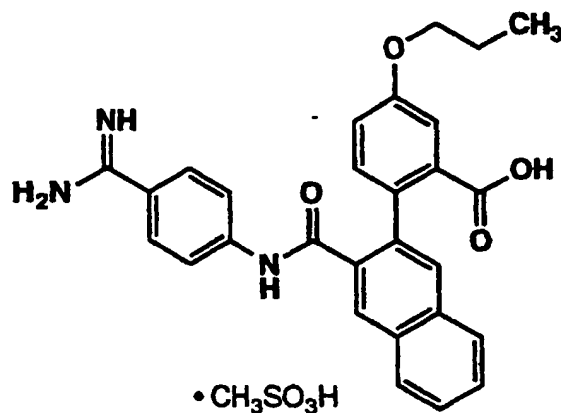
TLC : Rf 0.13 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d_6 -DMSO) : δ 12.7 (1H, brs), 10.63 (1H, s), 9.17 (2H, brs), 8.91 (2H, brs), 8.24 (1H, s), 8.11-8.05 (1H, m), 8.01-7.95 (1H, m), 7.77 (4H, s), 7.76 (1H, s), 7.65-7.59 (2H, m), 7.36 (1H, d, J = 2.5 Hz), 7.26 (1H, d, J = 8.5 Hz), 7.14 (1H, dd, J = 8.5 Hz, 2.5 Hz), 3.81 (3H, s), 2.35 (3H, s).

Example 19(101)

2-(3-(4-amidinophenylcarbamoyl)naphthalen-2-yl)-5-propoxybenzoic acid methanesulfonate

5 [0441]



25

TLC : R_f 0.20 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

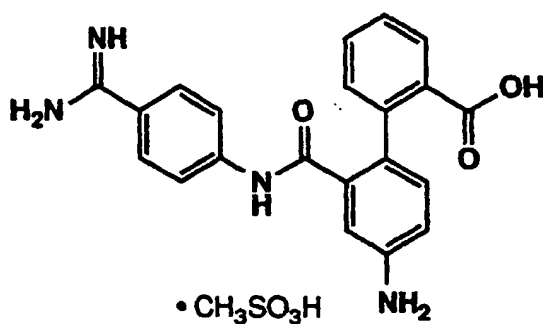
NMR (d₆-DMSO) : δ 12.7 (1H, brs), 10.63 (1H, s), 9.16 (2H, brs), 8.88 (2H, brs), 8.24 (1H, s), 8.10-8.05 (1H, m), 8.00-7.95 (1H, m), 7.77 (4H, s), 7.75 (1H, s), 7.67-7.59 (2H, m), 7.34 (1H, d, J = 2.5 Hz), 7.24 (1H, d, J = 8.0 Hz), 7.12 (1H, dd, J = 8.0 Hz, 2.5 Hz), 3.98 (2H, t, J = 7.0 Hz), 2.34 (3H, s), 1.74 (2H, sextet, J = 7.0 Hz), 0.98 (3H, t, J = 7.0 Hz).

30

Example 19(102)

35 2'-(4-amidinophenylcarbamoyl)-4'-amino-2-biphenylcarboxylic acid methanesulfonate

[0442]



50

55

TLC : R_f 0.22 (Chloroform : Methanol : Water = 7 : 3 : 0.3) ;

NMR (d₆-DMSO) : δ 10.49 (1H, s), 9.21 (2H, brs), 9.03 (2H, brs), 7.81 (1H, dd, J = 8.0 Hz, 1.5 Hz), 7.75 (2H, d, J = 9.0 Hz), 7.64 (2H, d, J = 9.0 Hz), 7.56-7.47 (2H, m), 7.44-7.35 (2H, m), 7.31 (1H, d, J = 8.0 Hz), 7.26 (1H, d, J =

8.0 Hz), 2.40 (3H, s).

Example 19(103)

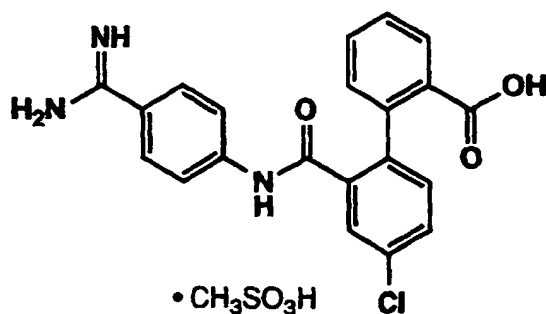
5 2'-(4-amidinophenylcarbamoyl)-4'-chloro-2-biphenylcarboxylic acid methanesulfonate

[0443]

10

15

20



25

TLC : Rf 0.48 (Chloroform : Methanol : Water = 7 : 3 : 0.3) ;
 NMR (d₆-DMSO) : δ 10.56 (1H, s), 9.14 (2H, s), 8.80 (2H, s), 7.85 (1H, dd, J = 1.8, 7.6 Hz), 7.73 (2H, d, J = 9.2 Hz), 7.71 (1H, d, J = 1.8 Hz), 7.68 (2H, d, J = 9.2 Hz), 7.61 (1H, dd, J = 1.8, 7.6 Hz), 7.54 (1H, dt, J = 1.8, 7.6 Hz), 7.42 (1H, dt, J = 1.8, 7.6 Hz), 7.29 (1H, d, J = 7.6 Hz), 7.24 (1H, dd, J = 1.8, 7.6 Hz), 2.33 (3H, s).

30 Example 19(104)

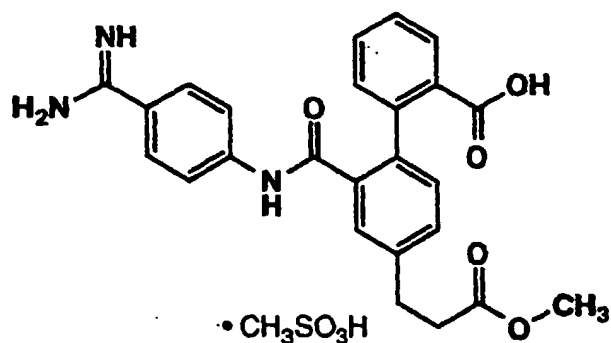
2'-(4-amidinophenylcarbamoyl)-4'-(2-methoxycarbonyl)ethyl-2-biphenylcarboxylic acid methanesulfonate

[0444]

35

40

45



50

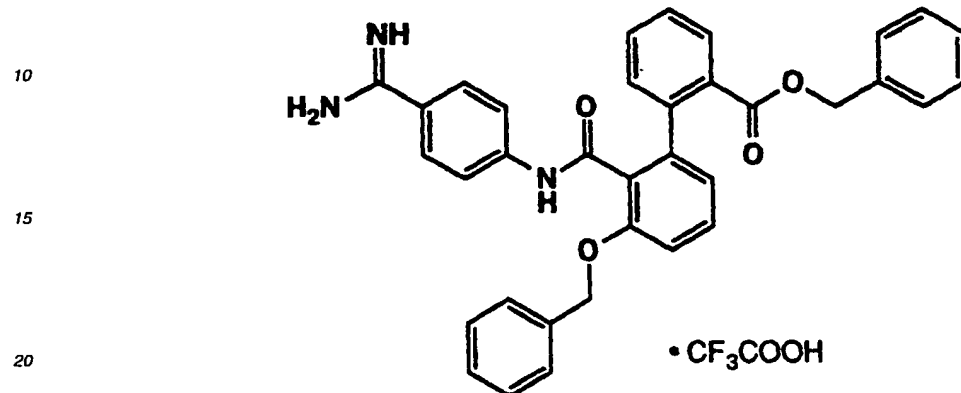
55

TLC : Rf 0.16 (Chloroform : Methanol = 4 : 1) ;
 NMR (d₆-DMSO) : δ 12.9-12.6 (1H, br), 10.4 (1H, s), 9.17 (2H, s), 9.0-8.8 (2H, br), 7.79 (1H, d, J = 7.8 Hz), 7.70 (2H, d, J = 6.8 Hz), 7.68 (1H, s), 7.67 (1H, t, J = 7.8 Hz), 7.51 (1H, d, J = 7.8 Hz), 7.5-7.3 (1H, m), 7.40 (2H, d, J = 6.8 Hz), 7.22 (1H, d, 7.8 Hz), 7.16 (1H, d, J = 7.8 Hz), 3.62 (3H, s), 2.99 (2H, t, J = 7.6 Hz), 2.75 (2H, t, J = 7.6 Hz), 2.34 (3H, s).

Example 19(105)

Benzyl 2'-(4-amidinophenylcarbamoyl)-3'-benzyloxy-2-biphenylcarboxylic acid trifluoroacetate

5 [0445]



25

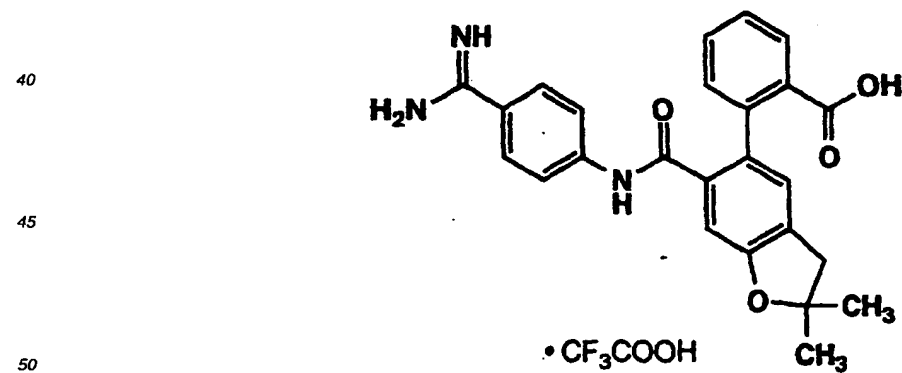
TLC : R_f 0.28 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;NMR (d₆-DMSO) : δ 10.53 (1H, s), 9.36 (2H, brs), 9.17 (2H, brs), 7.84 (1H, d, J = 8 Hz), 7.74 (2H, d, J = 9 Hz), 7.65 (2H, d, J = 9 Hz), 7.60-7.10 (15H, m), 6.86 (1H, d, J = 8 Hz), 5.20 (2H, s), 5.09 (2H, brs).

30

Example 19(106)

2-(2, 3-dihydro-2, 2-dimethyl-6-(4-amidinophenylcarbamoyl)benzofuran-5-yl)benzoic acid trifluoroacetate

35 [0446]



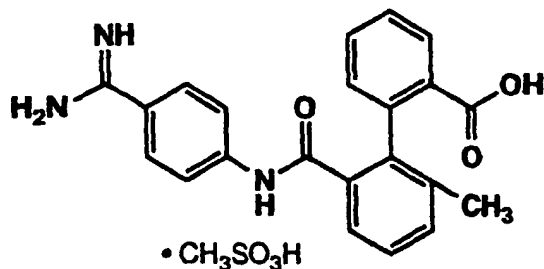
55

TLC : R_f 0.35 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;NMR (d₆-DMSO) : δ 10.59 (1H, brs), 9.19 (2H, s), 9.12 (2H, s), 7.72 (1H, d, J = 7 Hz), 7.71 (2H, d, J = 9 Hz), 7.62 (2H, d, J = 9 Hz), 7.42 (1H, t, J = 7 Hz), 7.33 (1H, t, J = 7 Hz), 7.16 (1H, d, J = 7 Hz), 7.02 (1H, s), 6.94 (1H, s), 3.07 (2H, s), 1.47 (6H, s).

Example 19(107)

2'-(4-amidinophenylcarbamoyl)-6'-methyl-2-biphenylcarboxylic acid methanesulfonate

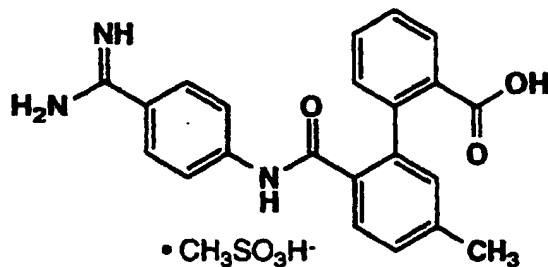
[0447]

TLC : R_f 0.21 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;NMR (d₆-DMSO) : δ 13.0-12.5 (1H, broad), 10.36 (1H, s), 9.12 (2H, brs), 8.89 (2H, brs), 7.86 (1H, d, J = 8 Hz), 7.70 (2H, d, J = 9 Hz), 7.60 (2H, d, J = 9 Hz), 7.57-7.35 (5H, m), 7.13 (1H, d, J = 8 Hz), 2.37 (3H, s), 1.96 (3H, s).

Example 19(108)

2'-(4-amidinophenylcarbamoyl)-5'-methyl-2-biphenylcarboxylic acid methanesulfonate

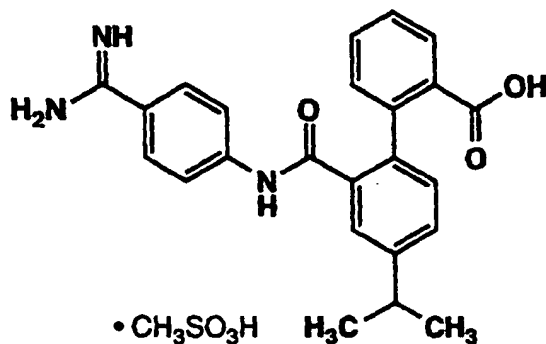
[0448]

TLC : R_f 0.14 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;NMR (d₆-DMSO) : δ 13.3-12.3 (1H, broad), 10.30 (1H, s), 9.14 (2H, brs), 8.91 (2H, brs), 7.79 (1H, dd, J = 8 Hz, 2 Hz), 7.73 (2H, d, J = 9 Hz), 7.66 (2H, d, J = 9 Hz), 7.58 (1H, d, J = 8 Hz), 7.51 (1H, td, J = 8 Hz, 2 Hz), 7.40 (1H, td, J = 8 Hz, 2 Hz), 7.31 (1H, d, J = 8 Hz), 7.21 (1H, d, J = 8 Hz), 7.06 (1H, s), 2.38 (6H, s).

Example 19(109)

2'-(4-amidinophenylcarbamoyl)-4'-isopropyl-2-biphenylcarboxylic acid methanesulfonate

5 [0449]



20

TLC : Rf 0.14 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

25 NMR (d₆-DMSO) : δ 13.3-12.5 (1H, broad), 10.55 (1H, s), 9.15 (2H, brs), 9.05 (2H, brs), 7.80-7.60 (5H, m), 7.52-7.32 (4H, m), 7.20 (1H, d, J = 8 Hz), 7.16 (1H, d, J = 8 Hz), 3.02 (1H, septet, J = 7 Hz), 2.38 (3H, s), 1.30 (6H, d, J = 7 Hz).

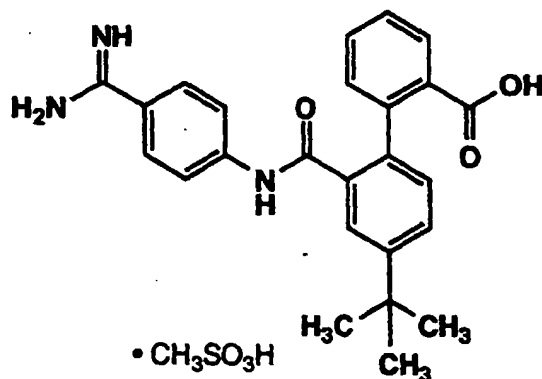
Example 19(110)

30

2'-(4-amidinophenylcarbamoyl)-4'-t-butyl-2-biphenylcarboxylic acid methanesulfonate

[0450]

35



45

50

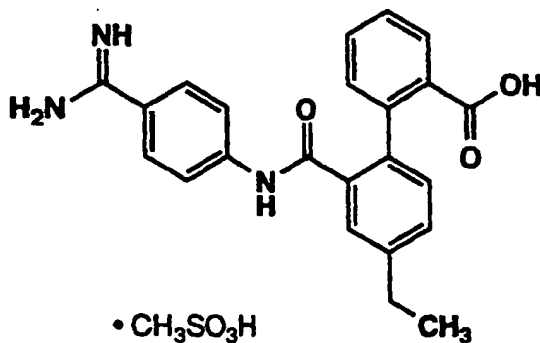
TLC : Rf 0.14 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

55 NMR (d₆-DMSO) : δ 13.0-12.6 (1H, broad), 10.35 (1H, s), 9.15 (2H, brs), 8.97 (2H, brs), 7.82-7.34 (9H, m), 7.24 (1H, d, J = 8 Hz), 7.19 (1H, d, J = 8 Hz), 2.37 (3H, s), 1.38 (9H, s).

Example 19(111)

2'-(4-amidinophenylcarbamoyl)-4'-ethyl-2-biphenylcarboxylic acid methanesulfonate

[0451]



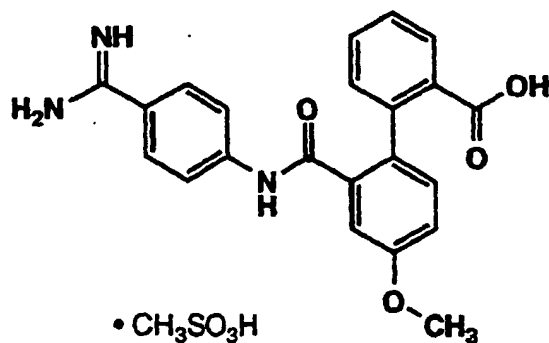
TLC : Rf 0.41 (Chloroform : Methanol : Water = 7 : 3 : 0.3) ;

NMR (d₆-DMSO) : δ 12.73 (1H, brs), 10.42 (1H, s), 9.12 (2H, brs), 8.84 (2H, brs), 7.77 (1H, dd, J = 7.6, 1.4 Hz), 7.74 (2H, d, J = 9.0 Hz), 7.65 (2H, d, J = 9.0 Hz), 7.54-7.30 (4H, m), 7.21 (1H, dd, J = 7.6, 1.2 Hz), 7.15 (1H, d, J = 7.6 Hz), 2.73 (2H, q, J = 7.6 Hz), 2.33 (3H, s), 1.26 (3H, t, J = 7.6 Hz).

Example 19(112)

2'-(4-amidinophenylcarbamoyl)-4'-methoxy-2-biphenylcarboxylic acid methanesulfonate

[0452]



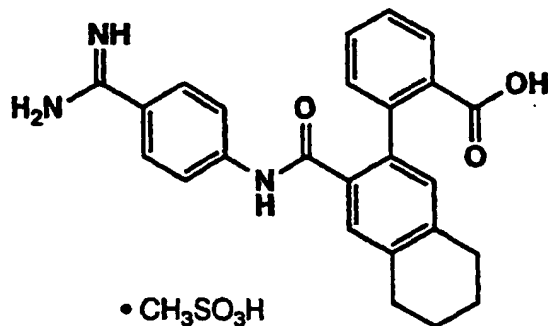
TLC : Rf 0.61 (Chloroform : Methanol : Water = 6 : 4 : 1) ;

NMR (d₆-DMSO) : δ 13.2-12.5 (1H, broad), 10.51 (1H, s), 9.26 (2H, brs), 9.05 (2H, brs), 7.88 (1H, dd, J = 8 Hz, 1 Hz), 7.85 (2H, d, J = 9 Hz), 7.77 (2H, d, J = 9 Hz), 7.59 (1H, td, J = 8 Hz, 1 Hz), 7.49 (1H, td, J = 8 Hz, 1 Hz), 7.32 (1H, dd, J = 8 Hz, 1 Hz), 7.30 (1H, d, J = 2 Hz), 7.23 (1H, d, J = 8 Hz), 7.21 (1H, dd, J = 8 Hz, 2 Hz), 3.97 (3H, s), 2.49 (3H, s).

Example 19(113)

2-(5, 6, 7, 8-tetrahydro-3-(4-amidinophenylcarbamoyl)naphthalen-2-yl)benzoic acid methanesulfonate

5 [0453]



20

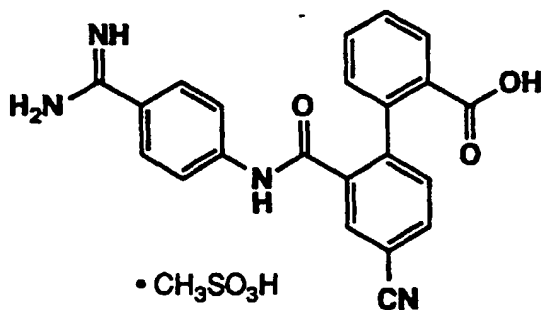
TLC : R_f 0.37 (Chloroform : Methanol : Water = 7 : 3 : 0.3) ;
 NMR (d₆-DMSO) : δ 13.0-12.6 (1H, broad), 10.32 (1H, s), 9.14 (2H, brs), 8.90 (2H, brs), 7.78 (1H, dd, J = 8 Hz, 2 Hz), 7.73 (2H, d, J = 9 Hz), 7.66 (2H, d, J = 9 Hz), 7.56-7.36 (3H, m), 7.19 (1H, dd, J = 8 Hz, 1 Hz), 6.92 (1H, s), 2.96-2.68 (4H, m), 2.37 (3H, s), 1.92-1.68 (4H, m).

25

Example 19(114)

30 2'-(4-amidinophenylcarbamoyl)-4'-cyano-2-biphenylcarboxylic acid methanesulfonate

[0454]



35

40

45

50 TLC : R_f 0.32 (Chloroform : Methanol : Water = 7 : 3 : 0.3) ;
 NMR (d₆-DMSO) : δ 13.0-12.5 (1H, broad), 10.66 (1H, s), 9.17 (2H, brs), 8.96 (2H, brs), 8.16 (1H, d, J = 1 Hz), 8.01 (1H, dd, J = 8 Hz, 2 Hz), 7.90 (1H, dd, J = 8 Hz, 1 Hz), 7.76 (2H, d, J = 9 Hz), 7.69 (2H, d, J = 9 Hz), 7.62-7.40 (3H, m), 7.26 (1H, dd, J = 8 Hz, 1 Hz), 2.39 (3H, s).

55

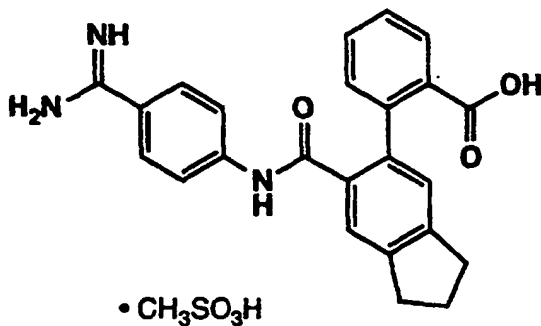
Example 19(115)

2-(6-(4-amidinophenylcarbamoyl)indan-5-yl)benzoic acid methanesulfonate

5 [0455]

10

15



20

TLC : Rf 0.29 (Chloroform : Methanol : Water = 7 : 3 : 0.3) ;

25 NMR (d₆-DMSO) : δ 12.9-12.6 (1H, broad), 10.32 (1H, s), 9.14 (2H, brs), 8.86 (2H, brs), 7.79 (1H, d, J = 8 Hz), 7.73 (2H, d, J = 9 Hz), 7.65 (2H, d, J = 9 Hz), 7.54-7.30 (3H, m), 7.19 (1H, d, J = 7 Hz), 7.08 (1H, s), 3.06-2.82 (4H, m), 2.35 (3H, s), 2.20-2.00 (2H, m).

Example 19(116)

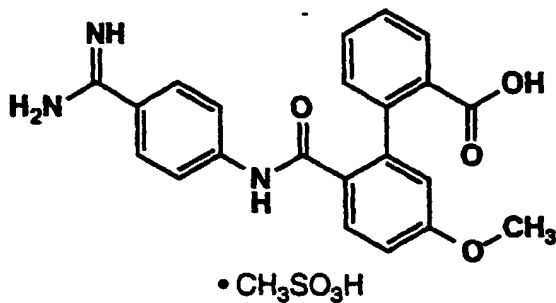
30

2'-(4-amidinophenylcarbamoyl)-5'-methoxy-2-biphenylcarboxylic acid methanesulfonate

[0456]

35

40



45

TLC : Rf 0.37 (Chloroform : Methanol : Water = 7 : 3 : 0.3) ;

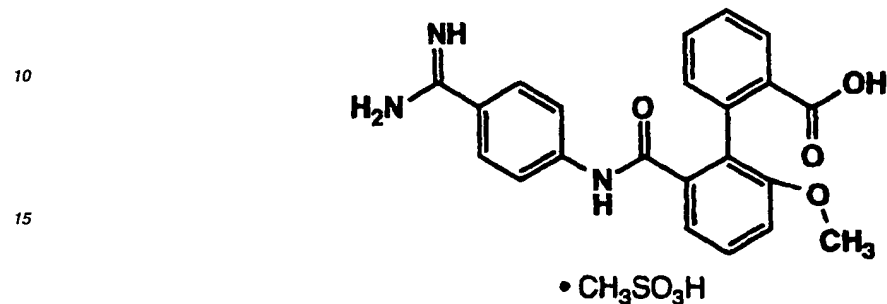
50 NMR (d₆-DMSO) : δ 10.23 (1H, s), 9.14 (2H, s), 8.79 (2H, s), 7.81 (1H, d, J = 7.4 Hz), 7.72 (2H, d, J = 8.8 Hz), 7.67 (1H, d, J = 7.4 Hz), 7.66 (2H, d, J = 8.8 Hz), 7.51 (1H, t, J = 7.4 Hz), 7.40 (1H, t, J = 7.4 Hz), 7.23 (1H, d, J = 7.4 Hz), 7.05 (1H, dd, J = 2.4, 7.4 Hz), 6.76 (1H, d, J = 2.4 Hz), 3.83 (3H, s), 2.33 (3H, s).

55

Example 19(117)

2'-(4-amidinophenylcarbamoyl)-6'-methoxy-2-biphenylcarboxylic acid methanesulfonate

5 [0457]



20

TLC : R_f 0.31 (Chloroform : Methanol : Water = 7 : 3 : 0.3) ;

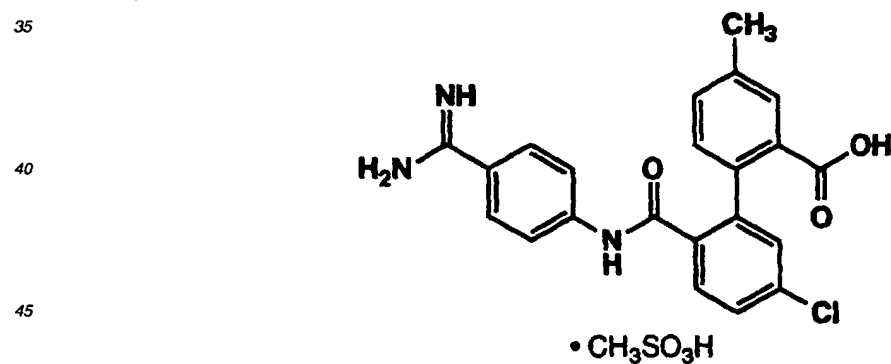
25 NMR (d₆-DMSO) : δ 10.32 (1H, s), 9.13 (2H, s), 8.82 (2H, s), 7.83 (1H, dd, J = 1.4, 7.6 Hz), 7.71 (2H, d, J = 9.0 Hz), 7.62 (2H, d, J = 9.0 Hz), 7.46 (1H, t, J = 8.0 Hz), 7.45 (1H, dt, J = 1.4, 7.6 Hz), 7.35 (1H, dt, J = 1.4, 7.6 Hz), 7.13-7.23 (3H, m), 3.67 (3H, s), 2.35 (3H, s).

Example 19(118)

30 2'-(4-amidinophenylcarbamoyl)-5'-chloro-4-methyl-2-biphenylcarboxylic acid methanesulfonate

[0458]

35



50

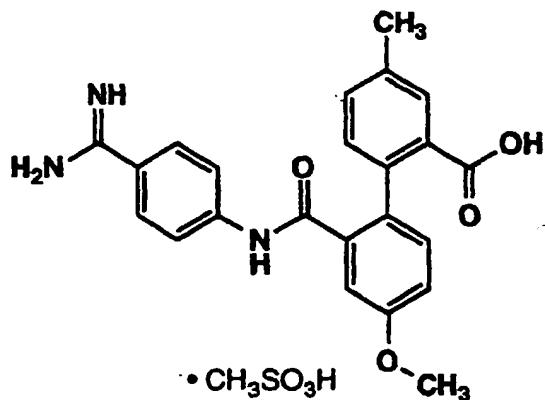
TLC : R_f 0.25 (Chloroform : Methanol : Acetic acid = 4 : 1 : 0.1) ;

55 NMR (d₆-DMSO) 13.2-12.0 (1H, br), 10.5 (1H, s), 9.15 (2H, s), 8.84 (2H, s), 7.8-7.5 (6H, m), 7.4-7.0 (1H, m), 7.35 (1H, d, J = 8.0 Hz), 7.28 (1H, s), 7.15 (1H, d, J = 7.6 Hz), 2.37 (3H, s), 2.35 (3H, s).

Example 19(119)

2'-(4-amidinophenylcarbamoyl)-4'-methoxy-4-methyl-2-biphenylcarboxylic acid methanesulfonate

[0459]

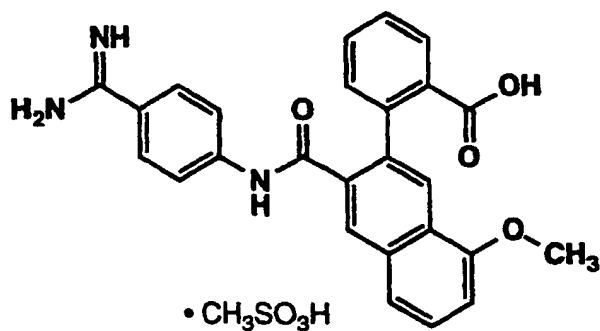
TLC : R_f 0.34 (Chloroform : Methanol : Acetic acid = 4 : 1 : 0.1) ;

NMR (d₆-DMSO) : δ 12.67 (1H, s), 10.40 (1H, s), 9.14 (2H, s), 8.83 (2H, s), 7.74 (2H, d, J = 9.4 Hz), 7.68 (2H, d, J = 9.4 Hz), 7.60 (1H, s), 7.29 (1H, dd, J = 8.4, 2.0 Hz), 7.18 (1H, d, J = 2.4 Hz), 7.1-7.0 (3H, m), 3.87 (3H, s), 2.36 (3H, s), 2.33 (3H, s).

Example 19(120)

2-(3-(4-amidinophenylcarbamoyl)-8-methoxynaphthalen-2-yl)benzoic acid methanesulfonate

[0460]

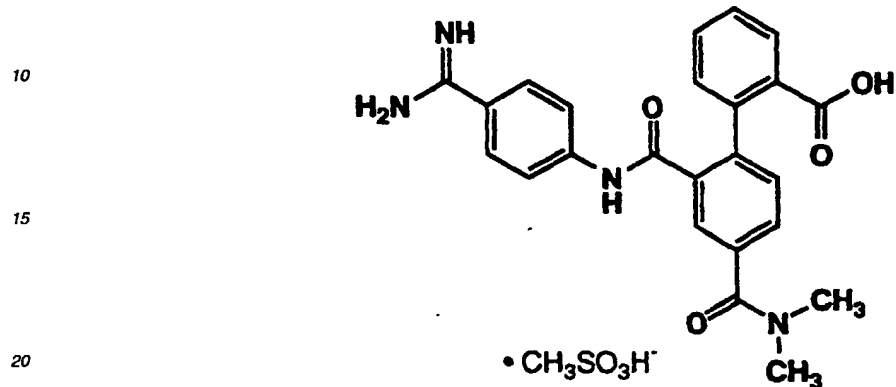
TLC : R_f 0.23 (Chloroform : Methanol : Water = 10 : 3 : 0.2) ;

NMR (d₆-DMSO) : δ 13.0-12.0 (1H, br), 10.65 (1H, s), 9.16 (2H, br.s), 8.84 (2H, br.s), 8.22 (1H, s), 7.92 (1H, s), 7.85 (1H, dd, J = 1.4, 7.4 Hz), 7.75 (4H, like s), 7.7-7.3 (4H, m), 7.32 (1H, dd, J = 1.4, 7.4 Hz), 7.09 (1H, d, J = 6.8 Hz), 3.96 (3H, s), 2.33 (3H, s).

Example 19(121)

2'-(4-amidinophenylcarbamoyl)-4'-dimethylcarbamoyl-2-biphenylcarboxylic acid methanesulfonate

5 [0461]



25

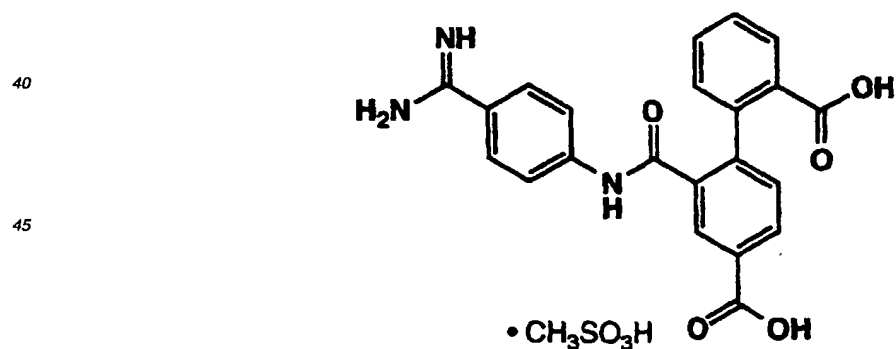
TLC : Rf 0.25 (Chloroform : Methanol : Water = 8 : 2 : 0.2) ;
 NMR (d_6 -DMSO) : δ 10.52 (1H, s), 9.16 (2H, s), 8.34 (2H, s), 7.85 (1H, dd, J = 1.4, 7.8 Hz), 7.74 (2H, d, J = 9.2 Hz),
 7.69 (2H, d, J = 9.2 Hz), 7.66 (1H, d, J = 1.8 Hz), 7.57 (1H, dd, J = 1.8, 7.8 Hz), 7.55 (1H, dt, J = 1.4, 7.8), 7.43 (1H,
 dt, J = 1.4, 7.8), 7.36 (1H, d, J = 7.8), 7.28 (1H, dd, J = 1.4, 7.8), 3.03 (6H, s), 2.34 (3H, s).

30

Example 19(122)

2'-(4-amidinophenylcarbamoyl)-2, 4'-biphenyldicarboxylic acid methanesulfonate

35 [0462]



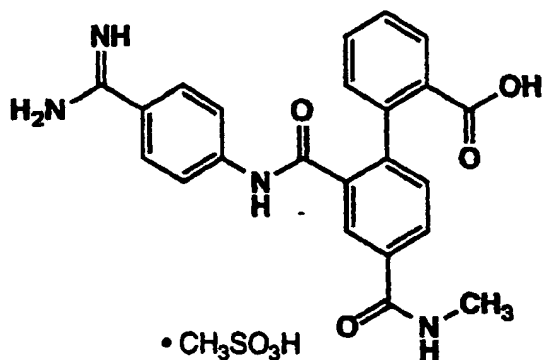
50

55 TLC : Rf 0.14 (Chloroform : Methanol : Water = 6 : 4 : 1) ;
 NMR (d_6 -DMSO) : δ 10.62 (1H, s), 9.15 (2H, s), 8.86 (2H, s), 8.19 (1H, s), 8.08 (1H, d, J = 7.8 Hz), 7.87 (1H, d, J
 = 7.2), 7.75 (2H, d, J = 9.0 Hz), 7.70 (2H, d, J = 9.0), 7.56 (1H, t, J = 7.2 Hz), 7.44 (1H, t, J = 7.2 Hz), 7.41 (1H, d,
 J = 7.8 Hz), 7.26 (1H, d, J = 7.2 Hz), 2.34 (3H, s).

Example 19(123)

2'-(4-amidinophenylcarbamoyl)-4'-methylcarbamoyl-2-biphenylcarboxylic acid methanesulfonate

[0463]

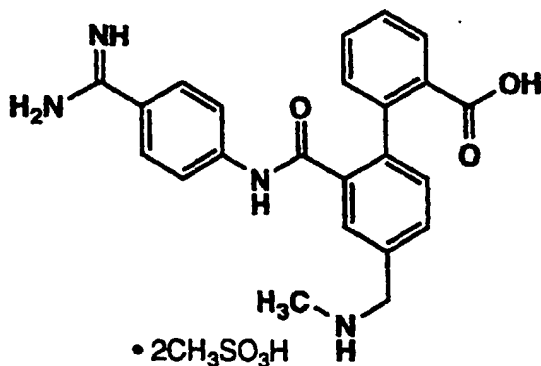
TLC : R_f 0.24 (Chloroform : Methanol : Water = 7 : 3 : 0.3) ;

NMR (d₆-DMSO) : δ 10.54 (1H, s), 9.15 (2H, s), 8.87 (2H, s), 8.62 (1H, br.q, J = 4.6 Hz), 8.13 (1H, d, J = 1.4 Hz), 7.99 (1H, dd, J = 1.4, 7.8 Hz), 7.86 (1H, dd, J = 1.4, 7.8 Hz), 7.76 (2H, d, J = 9.2 Hz), 7.71 (2H, d, J = 9.2 Hz), 7.54 (1H, dt, J = 1.4, 7.8 Hz), 7.43 (1H, dt, J = 1.4, 7.8 Hz), 7.35 (1H, d, J = 7.8 Hz), 7.25 (1H, dd, J = 1.4, 7.8 Hz), 2.85 (3H, br.d, J = 4.6 Hz), 2.39 (3H, s).

Example 19(124)

2'-(4-amidinophenylcarbamoyl)-4'-methyaminomethyl-2-biphenylcarboxylic acid dimethanesulfonate

[0464]

TLC : R_f 0.30 (Ethyl acetate : Acetic acid : Water = 3 : 1 : 1) ;

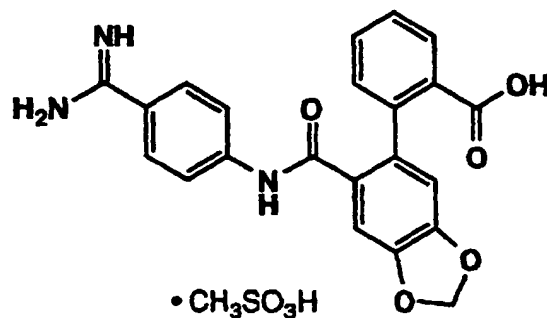
NMR (d₆-DMSO) : δ 10.41 (1H, s), 9.15 (2H, s), 8.89 (4H, s), 7.85 (1H, dd, J = 1.6, 7.8 Hz), 7.83 (1H, d, J = 1.6 Hz), 7.75 (2H, d, J = 9.2 Hz), 7.67 (2H, d, J = 9.2 Hz), 7.66 (1H, dd, J = 1.6, 7.8 Hz), 7.54 (1H, dt, J = 1.6, 7.8 Hz), 7.43 (1H, dt, J = 1.6, 7.8 Hz), 7.34 (1H, d, J = 7.8 Hz), 7.23 (1H, dd, J = 1.6, 7.8 Hz), 4.27 (2H, br.s), 2.65 (3H, t, J = 5.2).

Hz), 2.37 (6H, s).

Example 19(125)

2-(6-(4-amidinophenylcarbamoyl)-1, 2-methylenedioxybenzen-5-yl)benzoic acid methanesulfonate

[0465]

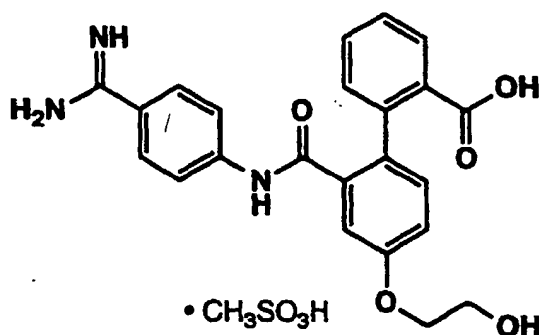


TLC : Rf 0.14 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;
NMR (d_6 -DMSO) : δ 13.0-12.5 (1H, broad), 10.20 (1H, s), 9.12 (2H, brs), 8.84 (2H, brs), 7.78 (1H, dd, J = 8.0 Hz, 1.5 Hz), 7.71 (2H, d, J = 9.0 Hz), 7.61 (2H, d, J = 9.0 Hz), 7.48 (1H, td, J = 7.5 Hz, 1.5 Hz), 7.37 (1H, td, J = 7.5 Hz, 1.5 Hz), 7.23 (1H, s), 7.21 (1H, dd, J = 7.5 Hz, 1.5 Hz), 6.80 (1H, s), 6.15 (2H, s), 2.34 (3H, s).

Example 19(126)

2'-(4-amidinophenylcarbamoyl)-4'-(2-hydroxyethoxy)-2-biphenylcarboxylic acid methanesulfonate

[0466]

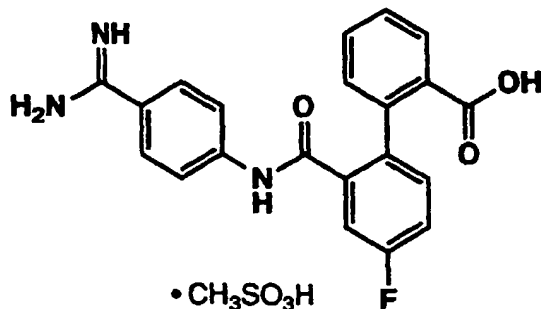


TLC : Rf 0.23 (Chloroform : Methanol : Water = 10 : 3 : 0.2) ;
NMR (d_6 -DMSO) : δ 13.0-11.8 (1H, br), 10.39 (1H, s), 9.13 (2H, br.s), 8.80 (2H, br.s), 7.8-7.6 (5H, m), 7.48 (1H, dt, J = 1.0, 7.2 Hz), 7.37 (1H, dt, J = 1.0, 7.2 Hz), 7.3-7.0 (4H, m), 4.10 (2H, t, J = 4.4 Hz), 3.76 (2H, t, J = 4.4 Hz), 3.8-3.3 (1H, br), 2.32 (3H, s).

Example 19(127)

2'-(4-amidinophenylcarbamoyl)-4'-fluoro-2-biphenylcarboxylic acid methanesulfonate

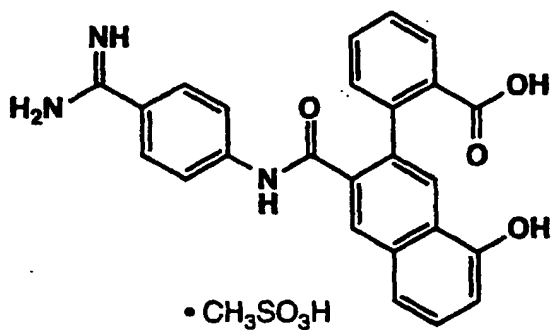
[0467]

TLC : R_f 0.47 (Chloroform : Methanol : Water = 7 : 3 : 0.3) ;NMR (d₆-DMSO) : δ 10.48 (1H, s), 9.15 (2H, s), 8.87 (2H, s), 7.84 (1H, dd, J = 1.6, 7.8 Hz), 7.74 (2H, d, J = 8.8 Hz), 7.67 (2H, d, J = 8.8 Hz), 7.24-7.56 (6H, m), 2.37 (3H, s).

Example 19(128)

2-(3-(4-amidinophenylcarbamoyl)-8-hydroxynaphthalen-2-yl)benzoic acid methanesulfonate

[0468]

TLC : R_f 0.23 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;NMR (d₆-DMSO) : δ 13.8-12.2 (1H, br), 10.62 (1H, s), 10.34 (1H, br.s), 9.17 (2H, br.s), 8.87 (2H, br.s), 8.16 (1H, s), 7.90 (1H, s), 7.84 (1H, d, J = 7.4 Hz), 7.75 (4H, like s), 7.6-7.2 (5H, m), 6.99 (1H, d, J = 6.4 Hz), 2.33 (3H, s).

Example 19(129)

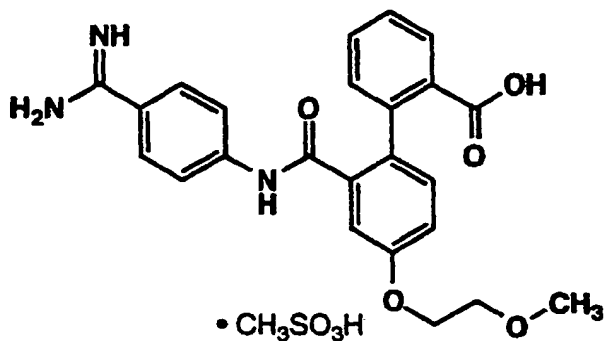
2'-(4-amidinophenylcarbamoyl)-4'-(2-methoxyethoxy)-2-biphenylcarboxylic acid methanesulfonate

5 [0469]

10

15

20



25

TLC : Rf 0.40 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d_6 -DMSO) : δ 13.2-11.6 (1H, br), 10.39 (1H, s), 9.13 (2H, s), 8.81 (2H, s), 7.8-7.6 (5H, m), 7.46 (1H, dt, J = 1.6, 7.4 Hz), 7.37 (1H, dt, J = 1.6, 7.4 Hz), 7.25-7.10 (4H, m), 4.21 (2H, t, J = 4.6 Hz), 3.70 (2H, t, J = 4.6 Hz), 3.33 (3H, s), 2.33 (3H, s).

30 Example 19(130)

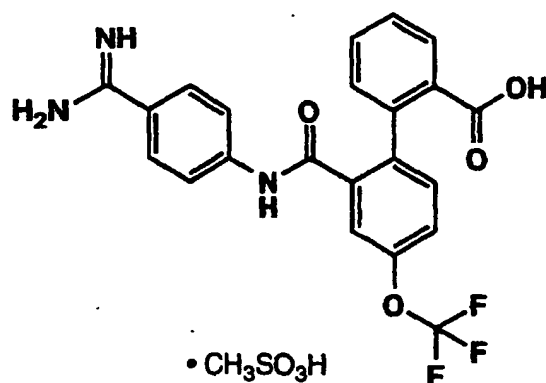
2'-(4-amidinophenylcarbamoyl)-4'-trifluoromethoxy-2-biphenylcarboxylic acid methanesulfonate

35 [0470]

40

45

50



55

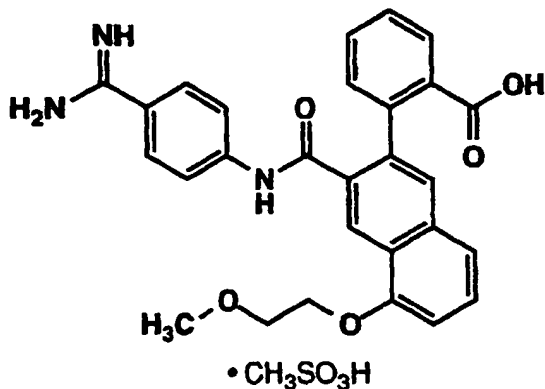
TLC : Rf 0.29 (Chloroform : Methanol : Water = 8 : 2 : 0.2) ;

NMR (d_6 -DMSO) : δ 10.5 (1H, s), 9.15 (2H, br s), 8.83 (2H, br s), 7.86 (1H, dd, J = 1.4, 7.0 Hz), 7.76-7.47 (8H, m), 7.41 (1H, d, J = 8.6 Hz), 7.29 (1H, dd, J = 1.4, 7.6 Hz), 2.36 (3H, s).

Example 19(131)

2-(3-(4-amidinophenylcarbamoyl)-5-(2-methoxyethoxy)naphthalen-2-yl)benzoic acid methanesulfonate

[0471]



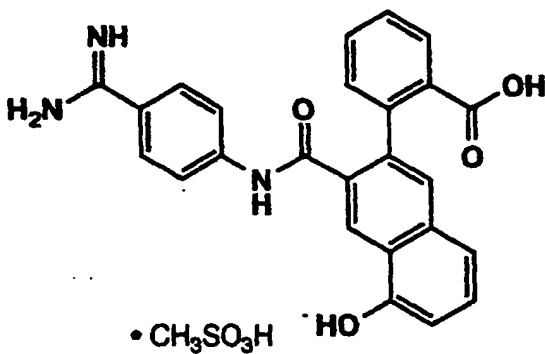
TLC : Rf 0.55 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d₆-DMSO) : δ 13.0-12.0 (1H, br), 10.61 (1H, s), 9.16 (2H, brs), 8.84 (2H, brs), 8.41 (1H, s), 7.85 (1H, d, J = 6.3 Hz), 7.8-7.6 (4H, m), 7.6-7.4 (4H, m), 7.43 (1H, t, J = 7.4 Hz), 7.33 (1H, d, J = 6.3 Hz), 7.10 (1H, t, J = 4.4 Hz), 4.36 (2H, t, J = 4.4 Hz), 3.83 (2H, t, J = 4.4 Hz), 3.37 (3H, s), 2.33 (3H, s).

Example 19(132)

2-(3-(4-amidinophenylcarbamoyl)-5-hydroxynaphthalen-2-yl)benzoic acid methanesulfonate

[0472]



TLC : Rf 0.53 (Ethyl acetate : Acetic acid : Water = 6 : 1 : 0.5) ;

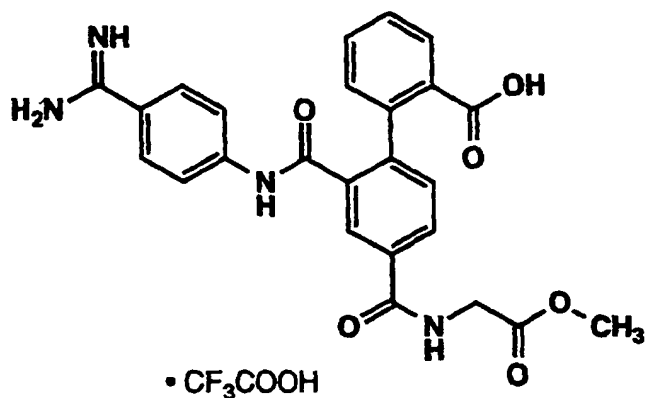
NMR (d₆-DMSO) : δ 13.0-12.0 (1H, br), 10.64 (1H, s), 10.48 (1H, br.s), 9.15 (2H, br.s), 8.85 (2H, br.s), 8.43 (1H, s), 7.85 (1H, br.d, J = 6.8 Hz), 7.51 (4H, like s), 7.67 (1H, s), 7.55 (1H, br.t, J = 6.4 Hz), 7.5-7.3 (3H, m), 7.32 (1H, d, J

= 9.4 Hz), 6.97 (1H, dd, J = 2.6, 6.0 Hz), 2.35 (3H, s).

Example 19(133)

2'-(4-amidinophenylcarbamoyl)-4'-((methoxycarbonylmethyl)carbamoyl)-2-biphenylcarboxylic acid trifluoroacetate

[0473]



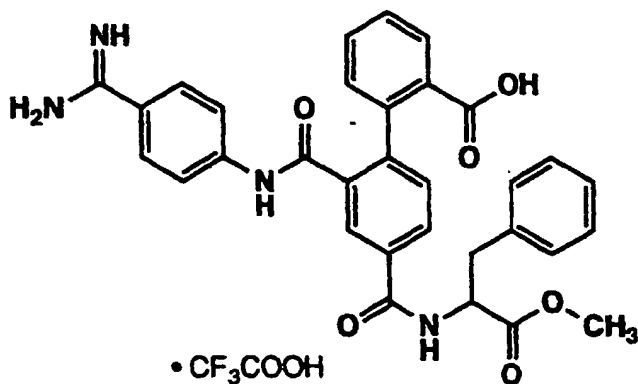
TLC : Rf 0.34 (Chloroform : Methanol : Water = 7 : 3 : 0.3) ;

NMR (CD₃OD) : δ 9.03 (1H, m), 8.19 (1H, d, J = 1.6 Hz), 8.02 (1H, dd, J = 1.6, 7.8 Hz), 7.92 (1H, dd, J = 1.6, 7.8 Hz), 7.70 (2H, d, J = 9.0 Hz), 7.62 (2H, d, J = 9.0 Hz), 7.53 (1H, dt, J = 1.6, 7.8 Hz), 7.43 (1H, dt, J = 1.6, 7.8 Hz), 7.37 (1H, d, J = 7.8 Hz), 7.28 (1H, dd, J = 1.6, 7.8 Hz), 4.16-4.18 (2H, m), 3.77 (3H, s).

Example 19(134)

2'-(4-amidinophenylcarbamoyl)-4'-((1-methoxycarbonyl-2-phenylethyl)carbamoyl)-2-biphenylcarboxylic acid trifluoroacetate

[0474]



EP 1 078 917 A1

TLC : Rf 0.60 (Chloroform : Methanol : Water = 7 : 3 : 0.3) ;

NMR (CD₃OD) : δ 8.84 (1H, br.d, J = 8.0 Hz), 8.06 (1H, s), 7.88-7.92 (2H, m), 7.70 (2H, d, J = 9.2 Hz), 7.61 (2H, d, J = 9.2 Hz), 7.39-7.56 (2H, m), 7.20-7.35 (7H, m), 4.92 (1H, m), 3.75 (3H, s), 3.08-3.38 (2H, m).

5 Example 19(135)

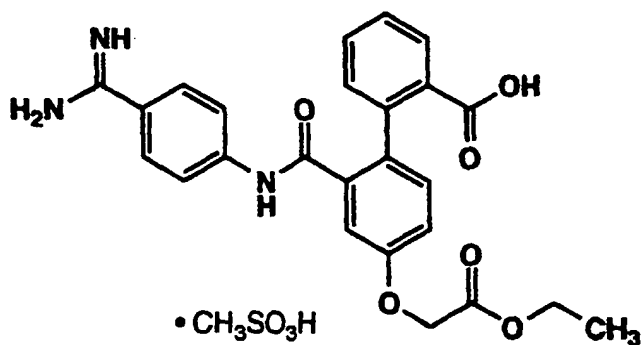
2'-(4-amidinophenylcarbamoyl)-4'-ethoxycarbonylmethoxy-2-biphenylcarboxylic acid methanesulfonate

[0475]

10

15

20



25

TLC : Rf 0.30 (Chloroform : Methanol : Water = 10 : 3 : 0.2) ;

NMR (d₆-DMSO) : δ 12.71 (1H, br), 10.38 (1H, s), 9.13 (2H, br.s), 8.77 (2H, br.s), 7.9-7.6 (5H, m), 7.49 (1H, m), 7.37 (1H, m), 7.3-7.0 (4H, m), 4.89 (2H, s), 4.20 (2H, q, J = 7.4 Hz), 2.31 (3H, s), 1.23 (3H, t, J = 7.4 Hz).

30

35

40

45

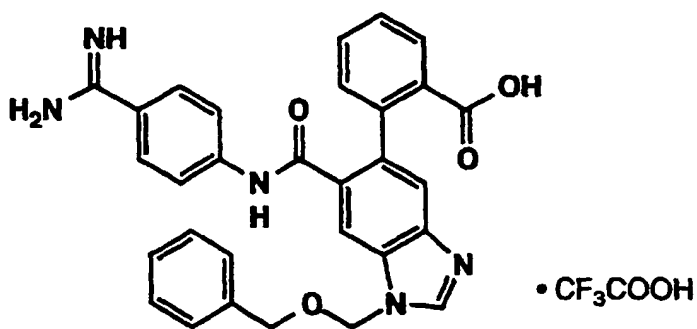
50

55

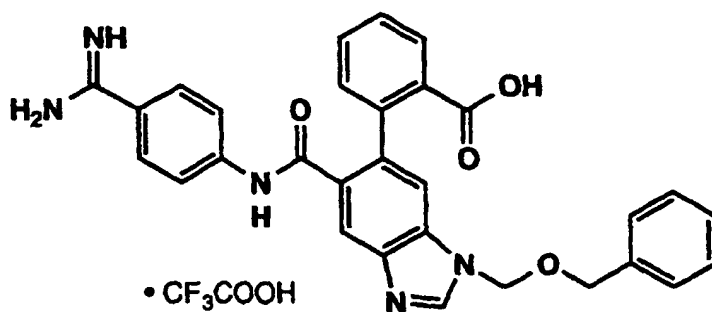
Example 19(136)

A mixture of 2-(6-(4-amidinophenylcarbamoyl)-1-benzyloxymethyl benzoimidazol-5-yl)benzoic acid trifluoroacetate and 2-(5-(4-amidinophenylcarbamoyl)-1-benzyloxymethylbenzoimidazol-6-yl)benzoic acid trifluoroacetate

[0476]



and



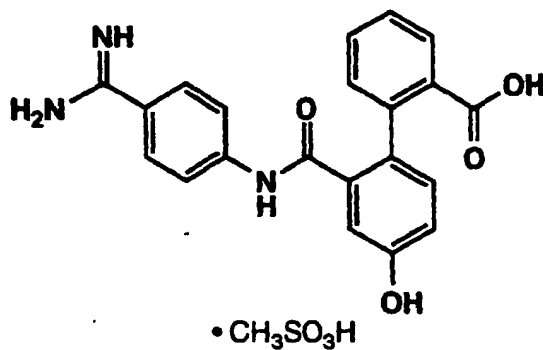
TLC : Rf 0.50 (Chloroform : Methanol : Water = 7 : 3 : 0.3) ;

NMR (CD₃OD) : δ 8.52 (0.5H, s), 8.47 (0.5H, s), 8.03 (0.5H, s), 8.01 (0.5H, s), 7.89 (0.5H, d, J = 8.0 Hz), 7.86 (0.5H, d, J = 8.0 Hz), 7.40-7.70 (7H, m), 7.24-7.28 (6H, m), 5.86 (1H, s), 5.75 (1H, s), 4.62 (1H, s), 4.60 (1H, s).

Example 19(137)

2'-(4-amidinophenylcarbamoyl)-4'-hydroxy-2-biphenylcarboxylic acid methanesulfonate

[0477]



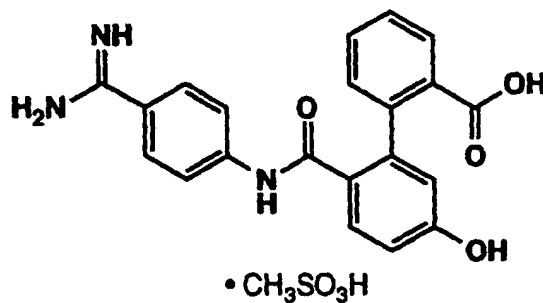
TLC : Rf 0.15 (Chloroform : Methanol : Water = 7 : 3 : 0.3) ;

NMR (d₆-DMSO) : δ 10.35 (1H, s), 9.92 (1H, s), 9.22 (2H, s), 8.97 (2H, s), 7.75 (2H, d, J = 8.8 Hz), 7.74 (1H, d, J = 7.6 Hz), 7.65 (2H, d, J = 8.8 Hz), 7.47 (1H, t, J = 7.6 Hz), 7.35 (1H, t, J = 7.6 Hz), 7.20 (1H, d, J = 7.6 Hz), 7.04 (1H, d, J = 8.6 Hz), 7.03 (1H, d, J = 2.4 Hz), 6.94 (1H, dd, J = 2.4, 8.6 Hz), 2.33 (3H, s).

Example 19(138)

2'-(4-amidinophenylcarbamoyl)-5'-hydroxy-2-biphenylcarboxylic acid methanesulfonate

[0478]



TLC : Rf 0.18 (Chloroform : Methanol : Water = 7 : 3 : 0.3) ;

NMR (d₆-DMSO) : δ 10.16 (1H, s), 10.15 (1H, s), 9.20 (2H, s), 8.96 (2H, s), 7.78 (1H, dd, J = 1.4, 7.6 Hz), 7.74 (2H, d, J = 9.0 Hz), 7.64 (2H, d, J = 9.0 Hz), 7.56 (1H, d, J = 8.4 Hz), 7.49 (1H, dt, J = 1.4, 7.6 Hz), 7.39 (1H, dt, J = 1.4, 7.6 Hz), 7.18 (1H, dd, J = 1.4, 7.6 Hz), 6.87 (1H, dd, J = 2.6, 8.4 Hz), 6.59 (1H, d, J = 2.6 Hz), 2.34 (3H, s).

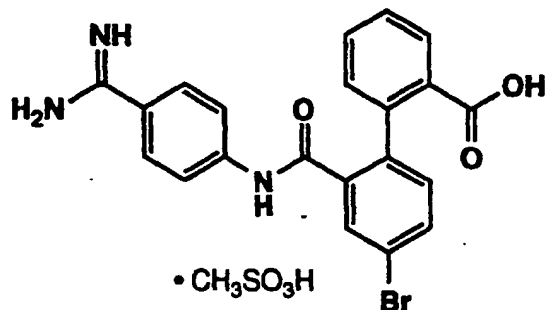
Example 19(139)

2'-(4-amidinophenylcarbamoyl)-4'-bromo-2-biphenylcarboxylic acid methanesulfonate

5 [0479]

10

15



20

TLC : Rf 0.23 (Chloroform : Methanol : Water = 8 : 2 : 0.2) ;

NMR (d₆-DMSO) : δ 10.58 (1H, s), 9.20 (2H, s), 8.93 (2H, s), 7.86 (1H, dd, J = 1.6, 7.8 Hz), 7.84 (1H, d, J = 1.6 Hz),
 25 7.74-7.78 (3H, m), 7.68 (2H, d, J = 9.2 Hz), 7.53 (1H, dt, J = 1.6, 7.8 Hz), 7.42 (1H, dt, J = 1.6, 7.8 Hz), 7.25 (1H, dd,
 J = 1.6, 7.8 Hz), 7.22 (1H, d, J = 8.4 Hz), 2.35 (3H, s).

Example 19(140)

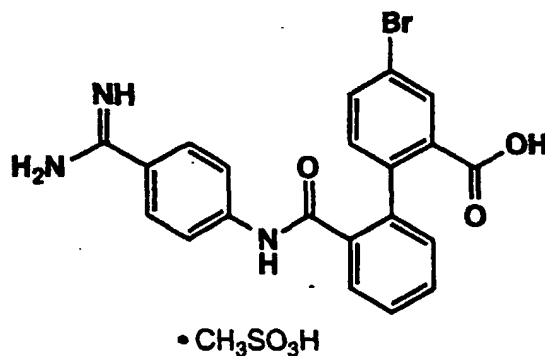
30 2'-(4-amidinophenylcarbamoyl)-4-bromo-2-biphenylcarboxylic acid methanesulfonate

[0480]

35

40

45



50

TLC : Rf 0.50 (Chloroform : Methanol : Water = 7 : 3 : 0.3) ;

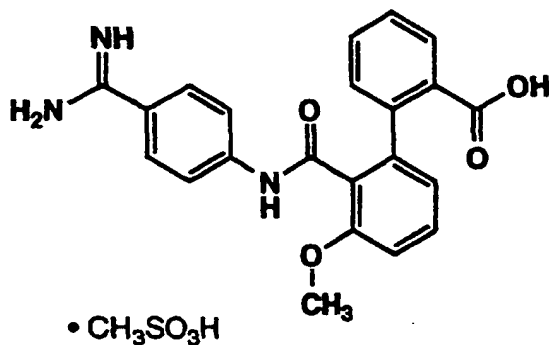
NMR (d₆-DMSO) : δ 10.53 (1H, s), 9.15 (2H, s), 8.79 (2H, s), 7.93-8.04 (3H, m), 7.74 (4H, s), 7.52-7.58 (2H, m),
 55 7.28 (1H, dd, J = 1.8, 7.6 Hz), 7.20 (1H, d, J = 8.4 Hz), 2.33 (3H, s).

55

Example 19(141)

2'-(4-amidinophenylcarbamoyl)-3'-methoxy-2-biphenylcarboxylic acid methanesulfonate

[0481]



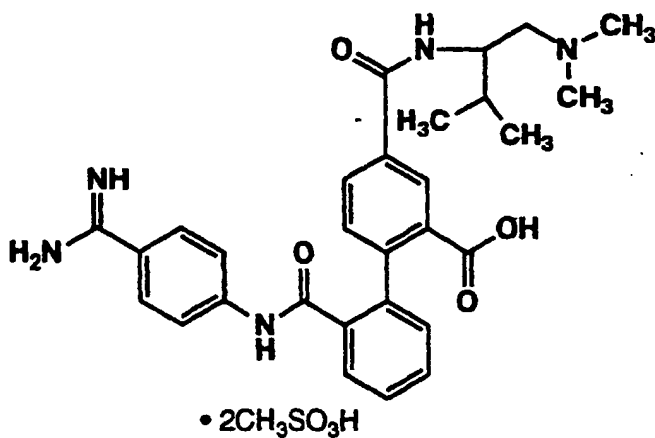
TLC : Rf 0.27 (Chloroform : Methanol : Water = 7 : 3 : 0.3) ;

NMR (d₆-DMSO) : δ 10.40 (1H, br.s), 9.14 (2H, s), 8.86 (2H, s), 7.78 (1H, dd, J = 1.8, 7.6 Hz), 7.70 (2H, d, J = 8.8 Hz), 7.61 (2H, d, J = 8.8 Hz), 7.27-7.47 (4H, m), 7.13 (1H, d, J = 8.0 Hz), 6.81 (1H, d, J = 7.6 Hz), 3.84 (3H, s), 2.34 (3H, s).

Example 19(142)

2'-(4-amidinophenylcarbamoyl)-4-((1-dimethylaminomethyl-2-methylpropyl) carbamoyl)-2-biphenylcarboxylic acid dimethanesulfonate

[0482]



TLC : Rf 0.48 (Ethyl acetate : Acetic acid : Water = 3 : 1 : 1) ;

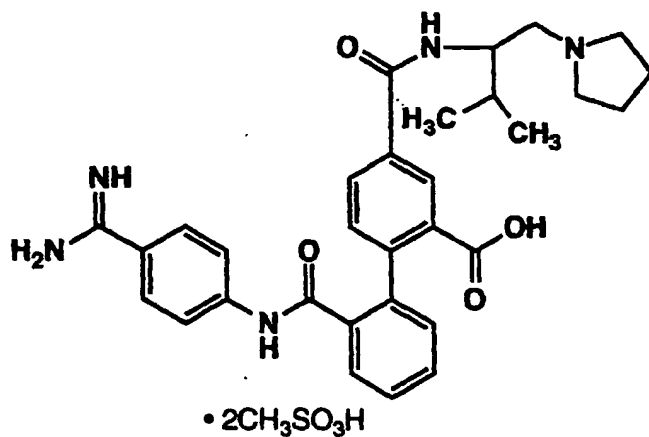
NMR (d₆-DMSO) : δ 12.8-12.2 (1H, br), 10.63 (1H, s), 9.21 (2H, s), 9.3-9.1 (1H, m), 9.00 (2H, s), 8.59 (1H, d, J =

9.2 Hz), 8.35 (1H, d, J = 2.0 Hz), 8.06 (1H, dd, J = 2.0, 8.0 Hz), 7.76 (4H, like s), 7.8-7.7 (1H, m), 7.7-7.5 (2H, m), 7.35 (1H, d, J = 8.0 Hz), 7.25 (1H, dd, J = 2.0, 8.0 Hz), 4.20 (1H, m), 3.4-3.2 (2H, m), 2.80 (3H, s), 2.78 (3H, s), 2.33 (6H, s), 1.84 (1H, m), 0.92 (3H, d, J = 7.4 Hz), 0.88 (3H, d, J = 7.4 Hz).

5 Example 19(143)

2'-(4-amidinophenylcarbamoyl)-4-((1-(pyrrolidin-1-ylmethyl)-2-methylpropyl) carbamoyl)-2-biphenylcarboxylic acid dimethanesulfonate

10 [0483]



30

TLC : Rf 0.50 (Ethyl acetate : Acetic acid : Water = 3 : 1 : 1) ;

NMR (d₆-DMSO) : δ 13.0-12.3 (1H, br), 10.61 (1H, br.s), 9.32 (1H, br), 9.17 (2H, br.s), 8.94 (2H, br.s), 8.53 (1H, br.d, J = 5.1 Hz), 8.36 (1H, d, J = 1.2 Hz), 8.05 (1H, dd, J = 1.2, 7.8 Hz), 7.75 (4H, like s), 7.8-7.6 (1H, m), 7.6-7.5 (2H, m), 7.35 (1H, d, J = 7.8 Hz), 7.24 (1H, dd, J = 1.2, 7.8 Hz), 4.18 (1H, m), 3.8-3.3 (4H, m), 3.2-3.0 (2H, m), 2.32 (6H, s), 2.1-1.8 (5H, m), 0.93 (3H, d, J = 6.6 Hz), 0.89 (3H, d, J = 6.6 Hz).

40

45

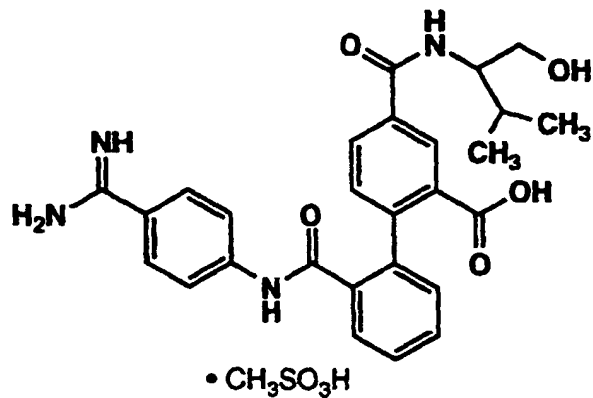
50

55

Example 19(144)

2'-(4-amidinophenylcarbamoyl)-4-((1-hydroxymethyl-2-methylpropyl) carbamoyl)-2-biphenylcarboxylic acid methanesulfonate

[0484]



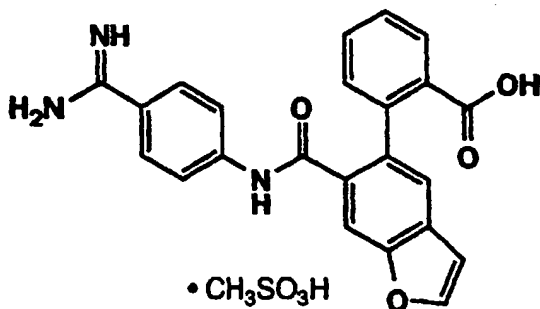
TLC: R_f 0.48 (Ethyl acetate : Acetic acid : Water = 3 : 1 : 0.5) ;

NMR (d₆-DMSO) : δ 13.0-12.4 (1H, br), 10.52 (1H, br), 9.15 (2H, s), 8.89 (2H, s), 8.30 (1H, d, J = 1.5 Hz), 8.17 (1H, br), 7.98 (1H, dd, J = 1.5, 8.0 Hz), 7.73 (4H, like s), 7.8-7.6 (1H, m), 7.6-7.4 (2H, m), 7.31 (1H, d, J = 8.0 Hz), 7.26 (1H, dd, J = 1.5, 8.0 Hz), 5.4-4.5 (1H, br), 3.81 (1H, m), 3.6-3.3 (2H, m), 2.36 (3H, s), 1.90 (1H, like sextet, J = 6.6 Hz), 0.90 (3H, d, J = 6.6 Hz), 0.87 (3H, d, J = 6.6 Hz).

Example 19(145)

2-(6-(4-amidinophenylcarbamoyl)benzofuran-5-yl)benzoic acid methanesulfonate

[0485]



TLC : R_f 0.23 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d₆-DMSO) : δ 13.0-12.6 (1H, broad), 10.42 (1H, s), 9.14 (2H, brs), 8.86 (2H, brs), 8.19 (1H, d, J = 2.0 Hz), 7.94 (1H, d, J = 1.0 Hz), 7.81 (1H, dd, J = 8.0 Hz, 1.5 Hz), 7.73 (2H, d, J = 9.0 Hz), 7.67 (2H, d, J = 9.0 Hz), 7.51

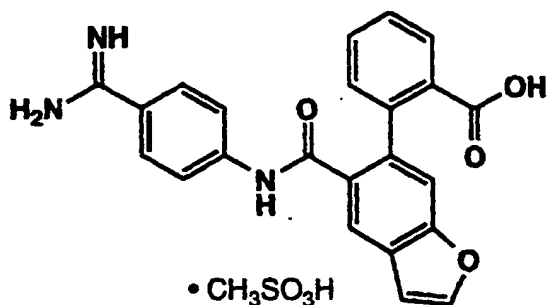
EP 1 078 917 A1

(1H, td, J = 8.0 Hz, 1.5 Hz), 7.50 (1H, s), 7.40 (1H, td, J = 8.0 Hz, 1.5 Hz), 7.27 (1H, dd, J = 8.0 Hz, 1.5 Hz), 7.05 (1H, dd, J = 2.0 Hz, 1.0 Hz), 2.34 (3H, s).

Example 19(146)

2-(5-(4-amidinophenylcarbamoyl)benzofuran-6-yl)benzoic acid methanesulfonate

[0486]



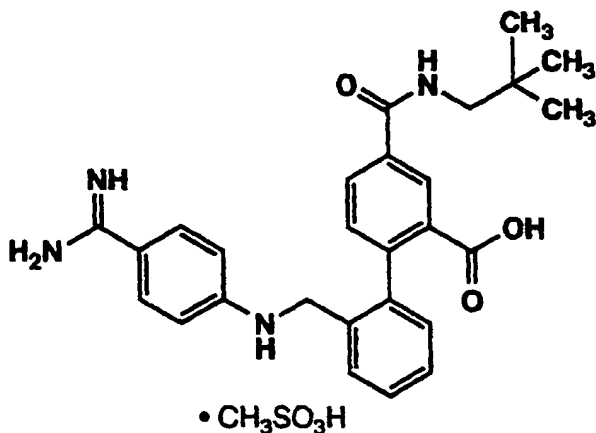
TLC : Rf 0.19 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d₆-DMSO) : δ 13.0-12.4 (1H, broad), 10.44 (1H, s), 9.14 (2H, brs), 8.86 (2H, brs), 8.14 (1H, d, J = 2.0 Hz), 7.98 (1H, s), 7.82 (1H, dd, J = 8.0 Hz, 1.5 Hz), 7.74 (2H, d, J = 9.0 Hz), 7.67 (2H, d, J = 9.0 Hz), 7.52 (1H, td, J = 8.0 Hz, 1.5 Hz), 7.48 (1H, d, J = 1.0 Hz), 7.40 (1H, td, J = 8.0 Hz, 1.5 Hz), 7.29 (1H, dd, J = 8.0 Hz, 1.5 Hz), 7.12 (1H, dd, J = 2.0 Hz, 1.0 Hz), 2.34 (3H, s).

Example 19(147)

2'-(4-amidinophenylaminomethyl)-4-((2, 2-dimethylpropyl)carbamoyl)-2-biphenylcarboxylic acid methanesulfonate

[0487]



TLC : Rf 0.32 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

EP 1 078 917 A1

NMR (d_6 -DMSO) : δ 12.97 (1H, br), 8.73 (2H, br.s), 8.56 (1H, br), 8.38 (2H, br.s), 8.36 (1H, d, $J = 1.8$ Hz), 8.04 (1H, dd, $J = 1.8, 7.8$ Hz), 7.53 (2H, d, $J = 8.4$ Hz), 7.43 (1H, d, $J = 8.4$ Hz), 7.4-7.2 (4H, m), 7.08 (1H, d, $J = 6.6$ Hz), 6.55 (2H, d, $J = 8.4$ Hz), 4.07 (2H, br.s), 3.13 (2H, d, $J = 6.6$ Hz), 2.34 (3H, s), 0.91 (9H, s).

5 Example 19(148)

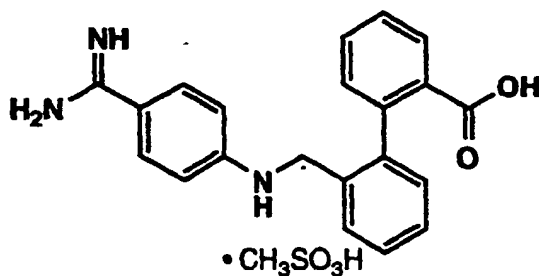
2'-(4-amidinophenylaminomethyl)-2-biphenylcarboxylic acid methanesulfonate

[0488]

10

15

20



25

TLC : R_f 0.51 (Chloroform : Methanol : Water = 7 : 3 : 0.3) ;
NMR (d_6 -DMSO) : δ 12.9-12.6 (1H, broad), 8.74 (2H, s), 8.42 (2H, s), 7.89 (1H, d, $J = 8$ Hz), 7.67-7.42 (4H, m), 7.40-7.18 (5H, m), 7.07 (1H, t, $J = 4$ Hz), 6.54 (2H, d, $J = 8$ Hz), 4.06 (2H, d, $J = 4$ Hz), 2.35 (3H, s).

Example 19(149)

30

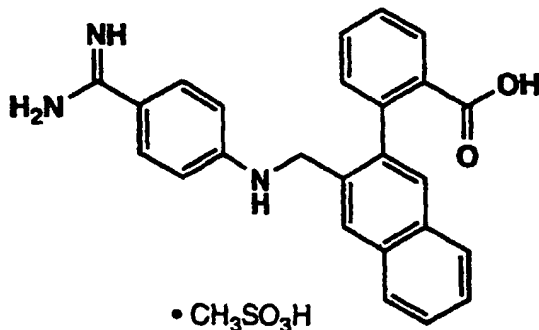
2-(3-(4-amidinophenylaminomethyl)naphthalen-2-yl)benzoic acid methanesulfonate

[0489]

35

40

45



50

TLC : R_f 0.21 (Chloroform : Methanol : Water = 10 : 3 : 0.2) ;
NMR (d_6 -DMSO) : δ 13.2-12.5 (1H, br), 8.74 (2H, br.s), 8.34 (2H, br.s), 8.0-7.4 (10H, m), 7.53 (2H, d, $J = 8.8$ Hz), 7.5-7.2 (1H, br), 6.59 (2H, d, $J = 8.8$ Hz), 4.18 (2H, br.s), 2.32 (3H, s).

55

Example 19(150)

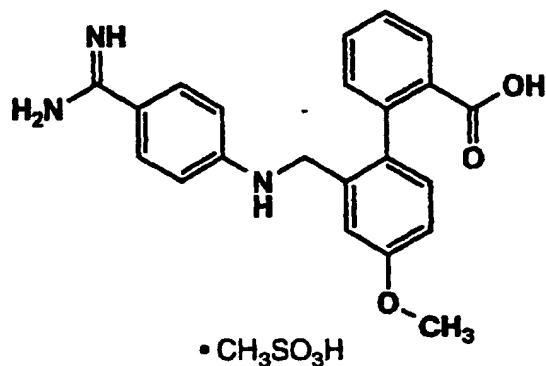
2'-(4-amidinophenylaminomethyl)-4'-methoxy-2-biphenylcarboxylic acid methanesulfonate

5 [0490]

10

15

20



25

TLC : R_f 0.37 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d₆-DMSO) : δ 13.1-12.5 (1H, broad), 8.75 (2H, brs), 8.44 (2H, brs), 7.85 (1H, dd, J = 7.5 Hz, 1.5 Hz), 7.61-7.43 (4H, m), 7.31 (1H, d, J = 7.5 Hz), 7.25 (1H, brs), 7.00 (1H, d, J = 9.0 Hz), 6.86-6.80 (2H, m), 6.54 (2H, d, J = 9.0 Hz), 4.02 (2H, brs), 3.70 (3H, s), 2.35 (3H, s).

30

Example 19(151)

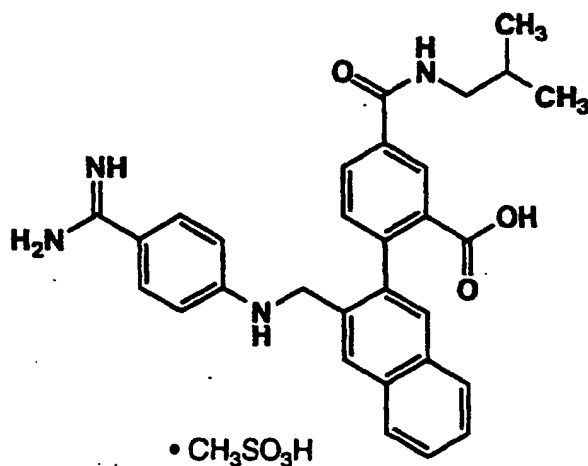
2-(3-(4-amidinophenylaminomethyl)naphthalen-2-yl)-5-((2-methylpropyl) carbamoyl)benzoic acid methanesulfonate

35 [0491]

40

45

50



55

TLC : R_f 0.30 (Chloroform : Methanol : Water = 8 : 2 : 0.2) ;

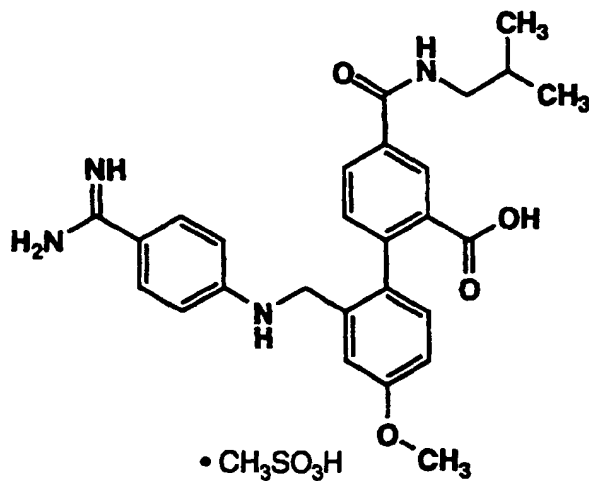
NMR (d₆-DMSO) : δ 8.74 (3H, br.s), 8.44 (1H, s), 8.31 (2H, s), 8.10 (1H, d, J = 8.0 Hz), 7.80-7.93 (2H, m), 7.75 (1H,

s), 7.64 (1H, s), 7.47-7.56 (5H, m), 7.34 (1H, br.s), 6.60 (2H, d, J = 8.8 Hz), 4.22 (2H, br.s), 3.14 (2H, t, J = 7.0 Hz), 2.32 (3H, s), 1.89 (1H, m), 0.92 (6H, d, J = 7.0 Hz).

Example 19(152)

2'-(4-amidinophenylaminomethyl)-4'-methoxy-4-((2-methylpropyl)carbamoyl)-2-biphenylcarboxylic acid methanesulfonate

[0492]



TLC : Rf 0.30 (Chloroform : Methanol : Water = 8 : 2 : 0.2) ;

NMR (d₆-DMSO) : δ 8.75 (2H, s), 8.67 (1H, t, J = 6.0 Hz), 8.34 (1H, d, J = 2.0 Hz), 8.31 (2H, s), 8.03 (1H, dd, J = 2.0, 8.0 Hz), 7.53 (2H, d, J = 8.8 Hz), 7.41 (1H, d, J = 8.0 Hz), 7.24 (1H, br.s), 7.02 (1H, d, J = 9.2 Hz), 6.86-6.88 (2H, m), 6.55 (2H, d, J = 8.8 Hz), 4.04 (2H, br.s), 3.72 (3H, s), 3.11 (2H, t, J = 6.0 Hz), 2.33 (3H, s), 1.87 (1H, m), 0.90 (6H, d, J = 6.6 Hz).

Example 19(153)

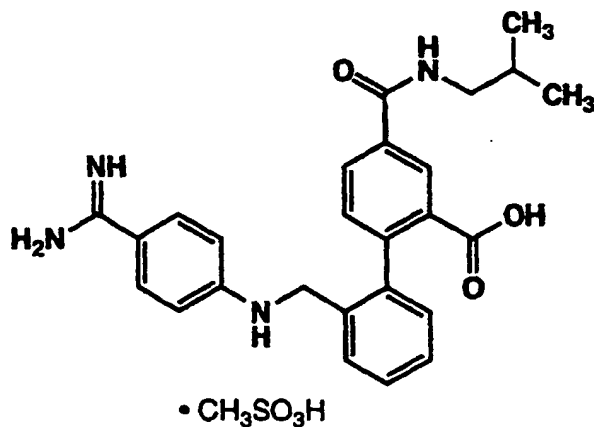
2'-(4-amidinophenylaminomethyl)-4-((2-methylpropyl)carbamoyl)-2-biphenylcarboxylic acid methanesulfonate

5 [0493]

10

15

20



25

TLC : R_f 0.42 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d₆-DMSO) : δ 10.4-9.6 (2H, broad), 8.60 (1H, brt, J = 6.0 Hz), 8.51 (2H, brs), 8.30 (1H, d, J = 2.0 Hz), 7.87 (1H, dd, J = 8.0 Hz, 2.0 Hz), 7.47 (2H, d, J = 9.0 Hz), 7.48-7.35 (1H, broad), 7.32-7.15 (4H, m), 7.03-6.96 (1H, m), 6.66 (2H, d, J = 9.0 Hz), 4.25-3.95 (2H, m), 3.08 (2H, t, J = 6.5 Hz), 2.34 (3H, s), 1.96-1.75 (1H, m), 0.88 (6H, d, J = 7.0 Hz).

30

Example 19(154)

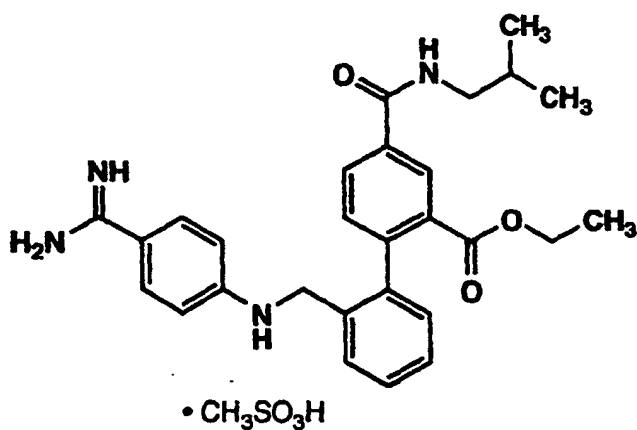
35 Ethyl 2'-(4-amidinophenylaminomethyl)-4-((2-methylpropyl)carbamoyl)-2-biphenylcarboxylate methanesulfonate

[0494]

40

45

50



55

EP 1 078 917 A1

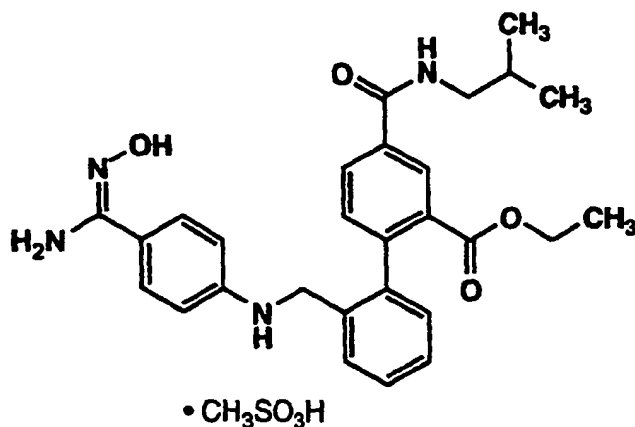
TLC : Rf 0.58 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d_6 -DMSO) : δ 8.70 (1H, brt, J = 6.0 Hz), 8.80-8.40 (4H, broad), 8.34 (1H, s), 8.07 (1H, d, J = 8.0 Hz), 7.54 (2H, d, J = 8.5 Hz), 7.50 (1H, d, J = 8.0 Hz), 7.40-7.17 (4H, m), 7.06 (1H, d, J = 7.5 Hz), 6.52 (2H, d, J = 8.5 Hz), 4.17-3.90 (4H, m), 3.11 (2H, t, J = 6.0 Hz), 2.32 (3H, s), 1.93-1.79 (1H, m), 0.91 (3H, t, J = 7.0 Hz), 0.89 (6H, d, J = 7.0 Hz).

Example 19(155)

Ethyl 2'-(4-(N²-hydroxyamidino)phenylaminomethyl)-4-((2-methylpropyl) carbamoyl)-2-biphenylcarboxylate methanesulfonate

[0495]



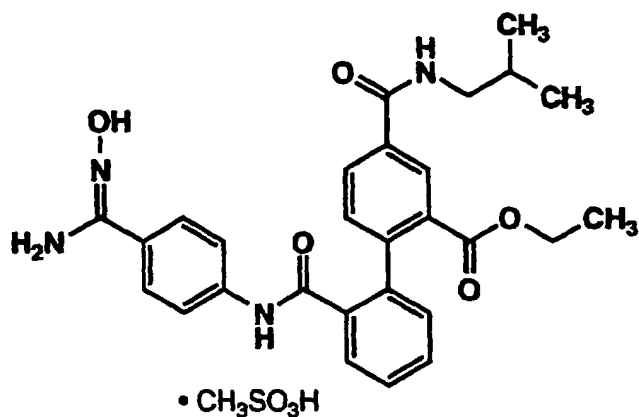
TLC : Rf 0.56 (Chloroform : Methanol : Water = 9 : 1 : 0.1) ;

NMR (d_6 -DMSO) : δ 12.26 (1H, brs), 11.2-10.3 (1H, broad), 8.93 (1H, brs), 8.73 (1H, brt, J = 6.0 Hz), 8.56 (1H, brs), 8.34 (1H, d, J = 2.0 Hz), 8.09 (1H, dd, J = 8.0 Hz, 2.0 Hz), 7.50 (1H, d, J = 8.0 Hz), 7.43 (2H, d, J = 9.0 Hz), 7.36-7.23 (3H, m), 7.06 (1H, d, J = 7.0 Hz), 6.52 (2H, d, J = 9.0 Hz), 4.16-3.90 (4H, m), 3.11 (2H, t, J = 6.0 Hz), 2.35 (3H, s), 1.97-1.76 (1H, m), 0.91 (3H, t, J = 7.0 Hz), 0.89 (6H, d, J = 7.0 Hz).

Example 19(156)

Ethyl 2'-(4-(N²-hydroxyamidino)phenylcarbamoyl)-4-((2-methylpropyl) carbamoyl)-2-biphenylcarboxylate methanesulfonate

[0496]



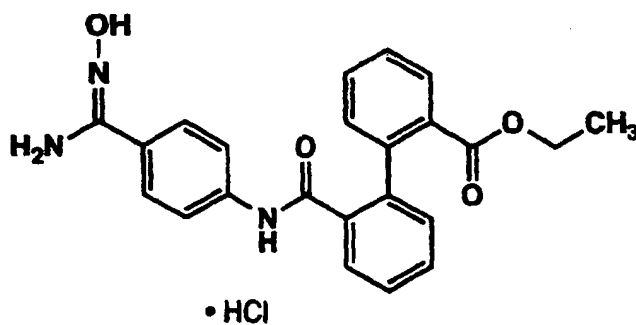
TLC : R_f 0.24 (Chloroform : Methanol = 10 : 1) ;

NMR (d₆-DMSO) : δ 12.60 (1H, br), 11.05 (1H, br), 10.53 (1H, s), 9.3-8.8 (2H, br), 8.66 (1H, t, J = 6.8 Hz), 8.22 (1H, d, J = 2.0 Hz), 8.02 (1H, dd, J = 2.0, 7.8 Hz), 7.8-7.5 (7H, m), 7.40 (1H, d, J = 7.8 Hz), 7.31 (1H, br.d, J = 7.8 Hz), 3.98 (2H, q, J = 7.4 Hz), 3.08 (2H, t, J = 6.8 Hz), 2.33 (3H, s), 1.84 (1H, like septet, J = 6.8 Hz), 0.90 (3H, t, J = 7.4 Hz), 0.88 (6H, d, J = 6.8 Hz).

Example 19(157)

Ethyl 2'-(4-(N²-hydroxyamidino)phenylcarbamoyl)-2-biphenylcarboxylate hydrochloride

[0497]



TLC : R_f 0.37 (Chloroform : Methanol : Water = 9 : 1 : 0.1) ;

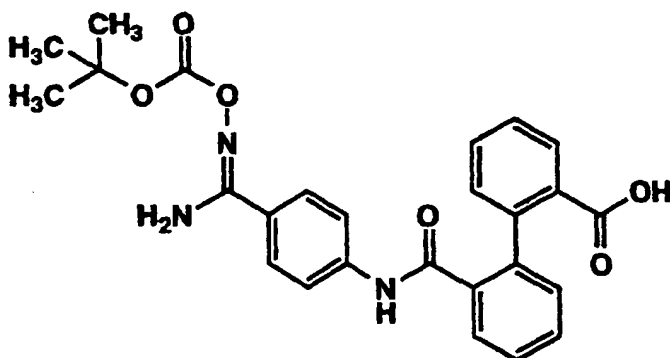
NMR (d₆-DMSO) : δ 11.16 (1H, brs), 10.42 (1H, s), 9.2-8.8 (3H, broad), 7.77 (1H, dd, J = 8.0 Hz, 1.5 Hz), 7.69 (2H, d, J = 9.0 Hz), 7.64 (2H, d, J = 9.0 Hz), 7.65-7.61 (1H, m), 7.59-7.48 (3H, m), 7.47 (1H, td, J = 8.0 Hz, 1.5 Hz), 7.34-

7.25 (2H, m), 3.96 (2H, q, J = 7.0 Hz), 0.88 (3H, t, J = 7.0 Hz).

Example 19(158)

2'-(4-(N²-t-butoxycarbonyloxyamidino)phenylcarbamoyl)-2-biphenylcarboxylic acid

[0498]



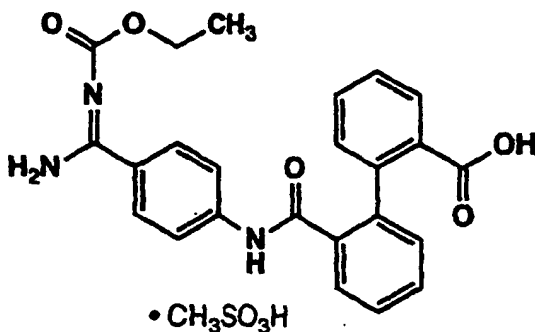
TLC : Rf 0.14 (Chloroform : Methanol : Water = 9 : 1 : 0.1) ;

NMR (d₆-DMSO) : δ 10.09 (1H, brs), 7.80 (1H, brd, J = 7.0 Hz), 7.70 - 7.30 (9H, m), 7.21 (2H, d, J = 8.5 Hz), 6.59 (2H, brs), 1.44 (9H, s).

Example 19(159)

2'-(4-(N²-ethoxycarbonylamidino)phenylcarbamoyl)-2-biphenylcarboxylic acid methanesulfonate

[0499]



TLC : Rf 0.72 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d₆-DMSO) : δ 13.0-12.0 (1H, br), 11.13 (1H, br), 10.46 (1H, s), 10.42 (1H, br.s), 7.81 (1H, dd, J = 1.0, 7.4 Hz), 7.8-7.6 (5H, m), 7.6-7.3 (4H, m), 7.3-7.2 (2H, m), 4.33 (2H, q, J = 7.4 Hz), 4.0-3.0 (1H, br), 2.30 (3H, s), 1.31 (3H, t, J = 7.4 Hz).

Example 19(160)

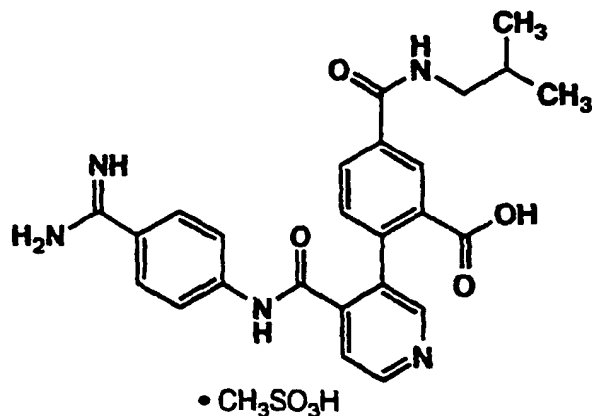
2-(4-(4-amidinophenylcarbamoyl)pyridin-3-yl)-5-((2-methylpropyl)carbamoyl) benzoic acid methanesulfonate

5 [0500]

10

15

20



25

TLC : R_f 0.50 (Chloroform : Methanol : Water = 7 : 3 : 0.3) ;

NMR (d₆-DMSO) : δ 11.03 (1H, s), 9.23 (2H, brs), 9.00 (2H, brs), 8.88 (1H, d, J = 5.5 Hz), 8.73 (1H, brt, J = 6.0 Hz), 8.71 (1H, s), 8.41 (1H, d, J = 2.0 Hz), 8.05 (1H, dd, J = 8.0 Hz, 2.0 Hz), 7.91 (1H, d, J = 5.5 Hz), 7.78 (2H, d, J = 9.5 Hz), 7.73 (2H, d, J = 9.5 Hz), 7.47 (1H, d, J = 8.0 Hz), 3.09 (2H, brt, J = 6.5 Hz), 2.36 (3H, s), 1.97-1.75 (1H, m), 0.88 (6H, d, J = 6.5 Hz).

30

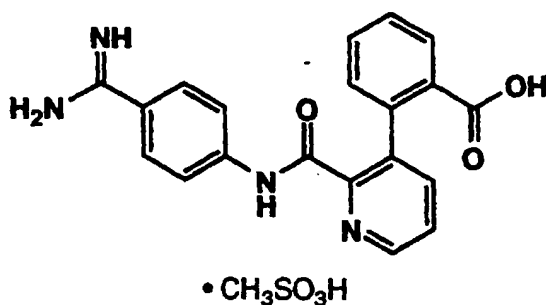
Example 19(161)

35 2-(2-(4-amidinophenylcarbamoyl)pyridin-3-yl)benzoic acid methanesulfonate

[0501]

40

45



50

55

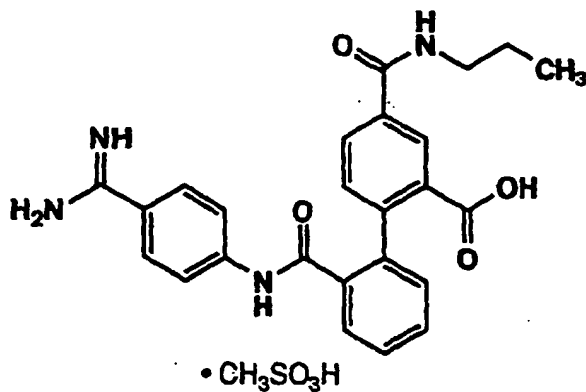
TLC : R_f 0.34 (Ethyl acetate : Acetic acid : Water = 3 : 1 : 0.5) ;

NMR (d₆-DMSO) : δ 10.96 (1H, s), 9.21 (2H, br.s), 8.96 (2H, br.s), 8.71 (1H, m), 7.94 (2H, d, J = 8.8 Hz), 8.0-7.8 (1H, m), 7.9-7.6 (2H, m), 7.77 (2H, d, J = 8.8 Hz), 7.60 (1H, t, J = 7.4 Hz), 7.48 (1H, t, J = 7.4 Hz), 7.24 (1H, d, J = 7.4 Hz), 5.6-4.2 (1H, br), 2.37 (3H, s).

Example 19(162)

2'-(4-amidinophenylcarbamoyl)-4-propylcarbamoyl-2-biphenylcarboxylic acid methanesulfonate

[0502]



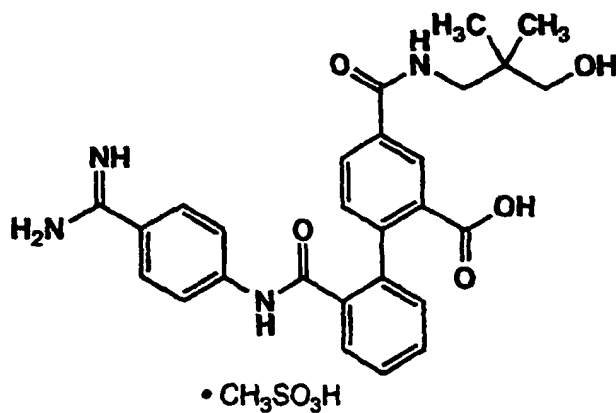
TLC : Rf 0.09 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d₆-DMSO) : δ 10.5 (1H, s), 9.13 (2H, br s), 8.79 (2H, br s), 8.64 (1H, t, J = 5.4 Hz), 8.29 (1H, d, J = 1.8 Hz), 7.96 (1H, dd, J = 1.8, 8.0 Hz), 7.80-7.60 (5H, m), 7.58-7.51 (2H, m), 7.32 (1H, d, J = 8.4 Hz), 7.30-7.20 (1H, m), 3.21 (2H, q, J = 6.6 Hz), 2.33 (3H, s), 1.52 (2H, sextet, J = 7.0 Hz), 0.88 (3H, t, J = 7.0 Hz).

Example 19(163)

2'-(4-amidinophenylcarbamoyl)-4-((3-hydroxy-2, 2-dimethylpropyl)carbamoyl)-2-biphenylcarboxylic acid methanesulfonate

[0503]



TLC : Rf 0.07 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

EP 1 078 917 A1

NMR (d_6 -DMSO) : δ 9.06 (4H, br s), 8.96 (1H, d, J = 8.0 Hz), 8.44 (1H, t, J = 5.4 Hz), 8.01 (1H, s), 7.70-7.50 (6H, m), 7.50-7.40 (2H, m), 7.10-7.00 (1H, m), 6.97 (1H, d, J = 8.0 Hz), 4.59 (1H, t, J = 5.8 Hz), 3.10-3.07 (4H, m), 2.31 (3H, s), 0.79 (6H, s).

5 Example 19(164)

2'-(4-amidinophenylcarbamoyl)-4-((1, 2, 2-trimethylpropyl)carbamoyl)-2-biphenylcarboxylic acid methanesulfonate

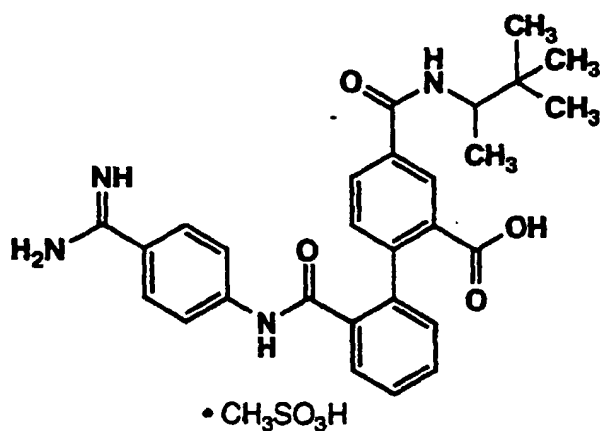
[0504]

10

15

20

25



30

TLC : R_f 0.42 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;
 NMR (d_6 -DMSO) : δ 10.54 (1H, s), 9.16 (2H, s), 8.83 (2H, s), 8.29 (1H, d, J = 1.8 Hz), 8.17 (1H, br.d, J = 9.4 Hz), 7.96 (1H, dd, J = 1.8, 8.0 Hz), 7.74 (4H, s), 7.71 (1H, dd, J = 1.8, 8.0 Hz), 7.52-7.59 (2H, m), 7.31 (1H, d, J = 8.0 Hz), 7.26 (1H, m), 3.98 (1H, m), 2.36 (3H, s), 1.09 (3H, d, J = 6.6 Hz), 0.91 (9H, s).

35

Example 19(165)

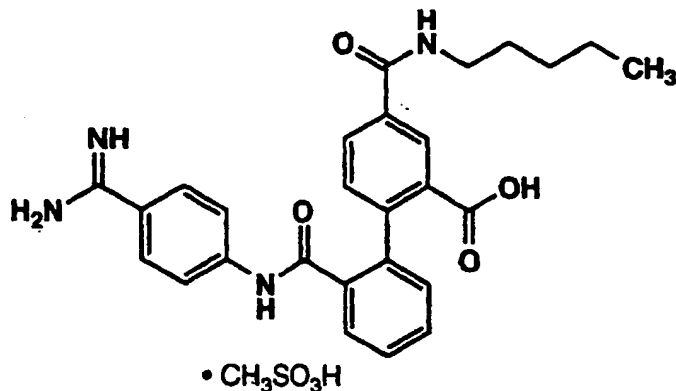
2'-(4-amidinophenylcarbamoyl)-4-pentylcarbamoyl-2-biphenylcarboxylic acid methanesulfonate

40 [0505]

45

50

55



EP 1 078 917 A1

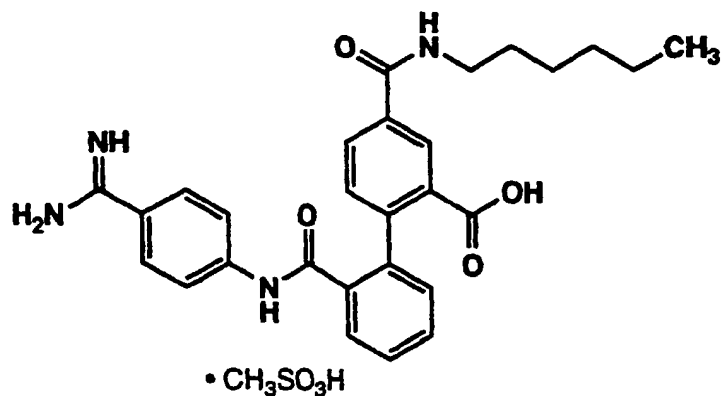
TLC : Rf 0.39 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d_6 -DMSO) : δ 10.52 (1H, s), 9.17 (2H, s), 8.89 (2H, s), 8.63 (1H, br.t, J = 6.0 Hz), 8.31 (1H, d, J = 1.8 Hz), 7.97 (1H, dd, J = 1.8, 8.0 Hz), 7.74 (4H, s), 7.71 (1H, dd, J = 1.8, 8.0 Hz), 7.52-7.59 (2H, m), 7.32 (1H, d, J = 8.0 Hz), 7.28 (1H, m), 3.26 (2H, dt, J = 6.0, 6.6 Hz), 2.36 (3H, s), 1.50-1.56 (2H, m), 1.26-1.33 (4H, m), 0.88 (3H, t, J = 6.6 Hz).

Example 19(166)

2'-(4-amidinophenylcarbamoyl)-4-hexylcarbamoyl-2-biphenylcarboxylic acid methanesulfonate

[0506]



TLC : Rf 0.26 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d_6 -DMSO) : δ 10.5 (1H, s), 9.14 (2H, br s), 8.84 (2H, br s), 8.62 (1H, t, J = 5.4 Hz), 8.28 (1H, d, J = 2.1 Hz), 7.95 (1H, dd, J = 2.1, 8.1 Hz), 7.75-7.67 (5H, m), 7.60-7.48 (2H, m), 7.31 (1H, d, J = 8.1 Hz), 7.28-7.25 (1H, m), 3.24 (2H, q, J = 6.3 Hz), 2.34 (3H, s), 1.58-1.42 (2H, m), 1.38-1.20 (6H, m), 0.85 (3H, t, J = 6.3 Hz).

Example 19(167)

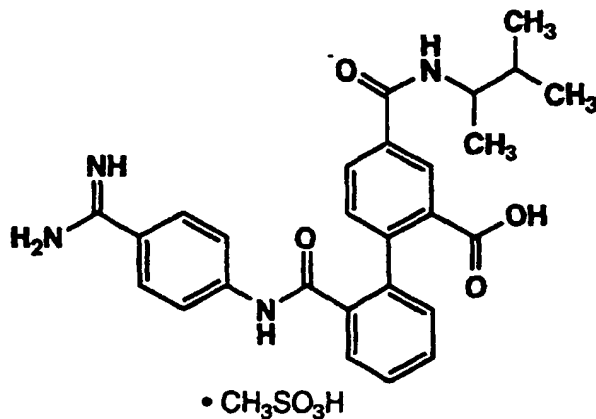
2'-(4-amidinophenylcarbamoyl)-4-((1, 2-dimethylpropyl)carbamoyl)-2-biphenylcarboxylic acid methanesulfonate

5 [0507]

10

15

20



25

TLC : R_f 0.23 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d₆-DMSO) : δ 10.5 (1H, s), 9.15 (2H, br s), 8.85 (2H, br s), 8.33 (1H, d, J = 9.0 Hz), 8.28 (1H, d, J = 1.8 Hz), 7.96 (1H, dd, J = 1.8, 7.8 Hz), 7.80-7.68 (5H, m), 7.60-7.49 (2H, m), 7.30 (1H, d, J = 7.8 Hz), 7.28-7.25 (1H, m), 3.88-3.77 (1H, m), 2.34 (3H, s), 1.75 (1H, sextet, J = 6.9 Hz), 1.09 (3H, d, J = 6.9 Hz), 0.88 (6H, dd, J = 2.7, 6.9 Hz).

30

Example 19(168)

2'-(4-amidinophenylcarbamoyl)-4-(((1S)-1-hydroxymethyl-2-methylpropyl)carbamoyl)-2-biphenylcarboxylic acid methanesulfonate

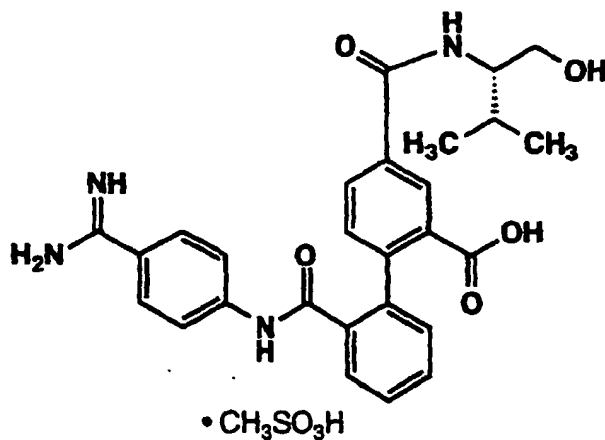
35

[0508]

40

45

50



55

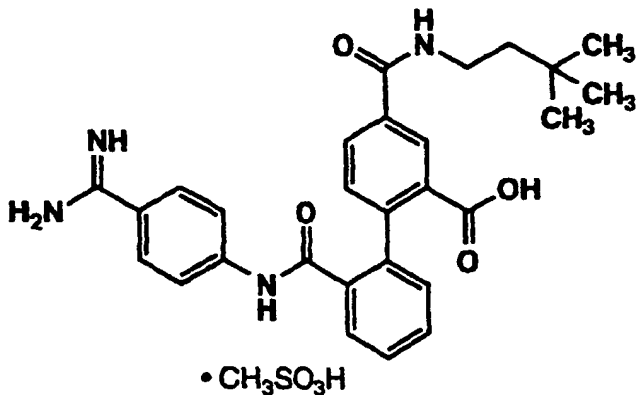
TLC : Rf 0.48 (Ethyl acetate : Acetic acid : Water = 3 : 1 : 0.5) ;

NMR (d_6 -DMSO) : δ 13.4-12.5 (1H, br), 10.54 (1H, s), 9.15 (2H, br.s), 8.91 (2H, br.s), 8.31 (1H, d, J = 1.4 Hz), 8.19 (1H, d, J = 8.8 Hz), 7.99 (1H, dd, J = 1.4, 8.0 Hz), 7.73 (4H, like s), 7.8-7.5 (1H, m), 7.6-7.4 (2H, m), 7.32 (1H, d, J = 8.0 Hz), 7.3-7.2 (1H, m), 5.2-3.6 (1H, br), 3.81 (1H, m), 3.6-3.4 (2H, m), 2.37 (3H, s), 1.90 (1H, like sextet, J = 6.8 Hz), 0.90 (3H, d, J = 6.8 Hz), 0.86 (3H, d, J = 6.8 Hz).

Example 19(169)

2'-(4-amidinophenylcarbamoyl)-4-((3, 3-dimethylbutyl)carbamoyl)-2-biphenylcarboxylic acid methanesulfonate

[0509]



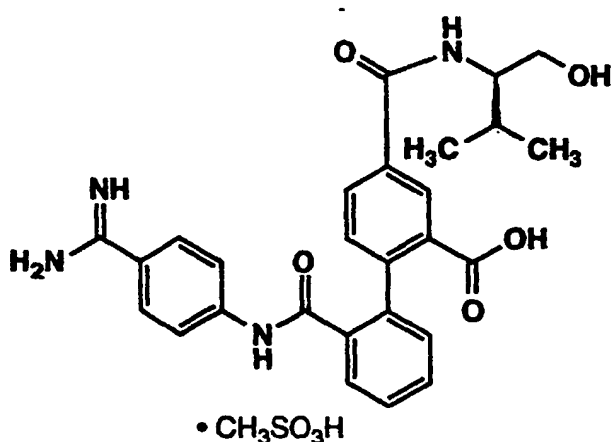
TLC : Rf 0.44 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d_6 -DMSO) : δ 12.83 (1H, br.s), 10.53 (1H, s), 9.18 (2H, s), 8.92 (2H, s), 8.61 (1H, br.t, J = 6.0 Hz), 8.29 (1H, d, J = 1.8 Hz), 7.95 (1H, dd, J = 1.8, 8.0 Hz), 7.74 (4H, s), 7.70 (1H, dd, J = 1.8, 8.0 Hz), 7.51-7.60 (2H, m), 7.32 (1H, d, J = 8.0 Hz), 7.28 (1H, dd, J = 1.8, 8.0 Hz), 3.25-3.35 (2H, m), 2.36 (3H, s), 1.43-1.49 (2H, m), 0.93 (9H, s).

Example 19(170)

2'-(4-amidinophenylcarbonyl)-4-(((1R)-1-hydroxymethyl-2-methylpropyl) carbonyl)-2-biphenylcarboxylic acid methanesulfonate

[0510]



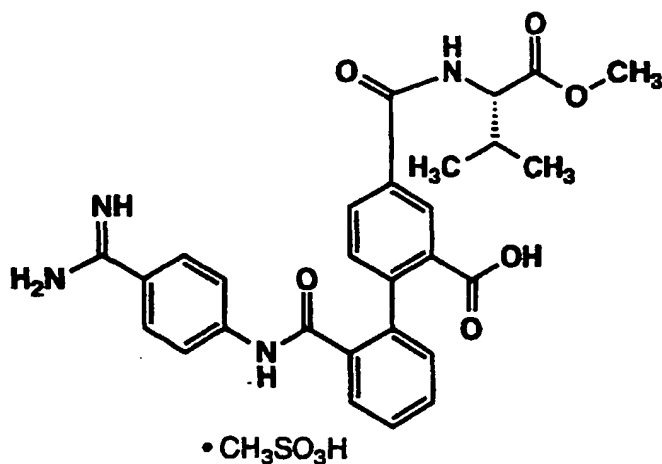
TLC : R_f 0.48 (Ethyl acetate : Acetic acid : Water = 3 : 1 : 0.5) ;

NMR (d₆-DMSO) : δ 12.4-11.6 (1H, br), 10.54 (1H, s), 9.15 (2H, br.s), 8.89 (2H, br.s), 8.30 (1H, d, J = 1.8 Hz), 8.19 (1H, d, J = 9.0 Hz), 7.98 (1H, dd, J = 1.8, 8.1 Hz), 7.73 (4H, like s), 7.8-7.6 (1H, m), 7.65-7.45 (2H, m), 7.31 (1H, d, J = 8.1 Hz), 7.26 (1H, dd, J = 1.8, 8.1 Hz), 4.5-3.8 (1H, br), 3.81 (1H, m), 3.6-3.4 (2H, m), 2.36 (3H, s), 1.90 (1H, like sextet, J = 6.9 Hz), 0.89 (3H, d, J = 6.9 Hz), 0.86 (3H, d, J = 6.9 Hz).

Example 19(171)

2'-(4-amidinophenylcarbonyl)-4-(((1S)-1-methoxycarbonyl-2-methylpropyl) carbonyl)-2-biphenylcarboxylic acid methanesulfonate

[0511]



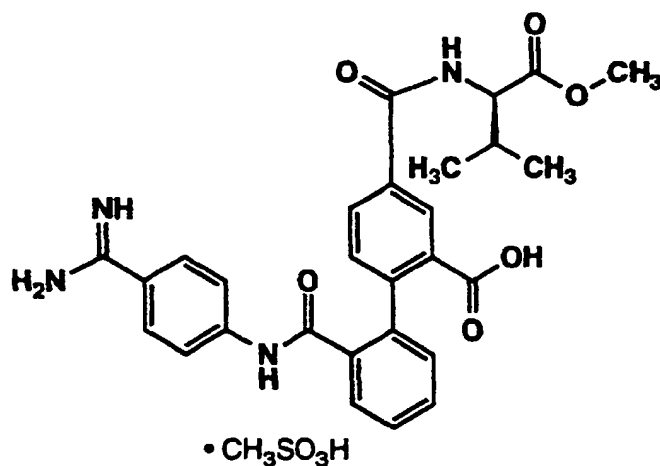
TLC : Rf 0.36 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d_6 -DMSO) : δ 10.5 (1H, s), 9.14 (2H, br s), 8.85 (1H, d, J = 7.6 Hz), 8.83 (2H, br s), 8.33 (1H, d, J = 1.8 Hz),
 8.01 (1H, dd, J = 1.8, 8.0 Hz), 7.80-7.68 (5H, m), 7.59-7.52 (2H, m), 7.33 (1H, d, J = 8.0 Hz), 7.30-7.25 (1H, m), 4.30
 (1H, t, J = 7.4 Hz), 3.65 (3H, s), 2.32 (3H, s), 2.32-2.10 (1H, m), 0.98-0.91 (6H, m).

Example 19(172)

2'-(4-amidinophenylcarbamoyl)-4-(((1R)-1-methoxycarbonyl-2-methylpropyl) carbamoyl)-2-biphenylcarboxylic acid
 methanesulfonate

[0512]



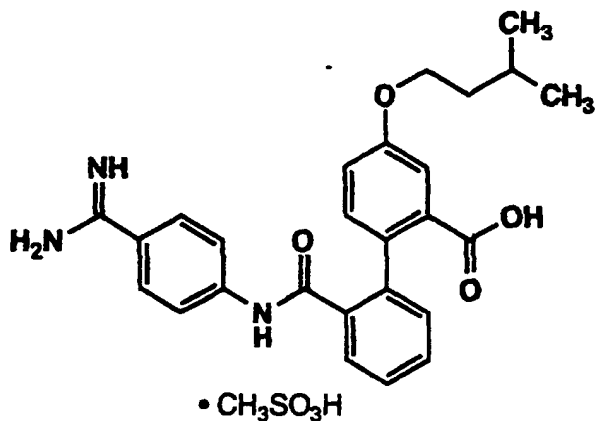
TLC : Rf 0.36 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d_6 -DMSO) : δ 10.5 (1H, s), 9.15 (2H, br s), 8.85 (1H, d, J = 7.4 Hz), 8.83 (2H, br s), 8.33 (1H, d, J = 1.8 Hz);
 8.01 (1H, dd, J = 1.8, 8.0 Hz), 7.80-7.68 (5H, m), 7.59-7.50 (2H, m), 7.33 (1H, d, J = 8.0 Hz), 7.30-7.25 (1H, m),
 4.30 (1H, t, J = 7.8 Hz), 3.65 (3H, s), 2.33 (3H, s), 2.33-2.10 (1H, m), 0.98-0.91 (6H, m).

Example 19(173)

2'-(4-amidinophenylcarbamoyl)-4-(3-methylbutoxy)-2-biphenylcarboxylic acid methanesulfonate

5 [0513]



25

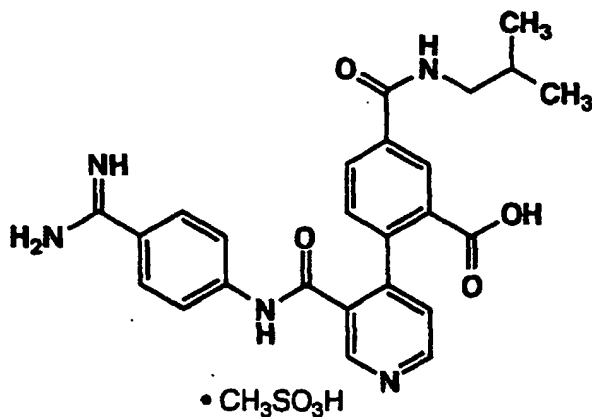
TLC : Rf 0.26 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d₆-DMSO) : δ 10.4 (1H, s), 9.14 (2H, br s), 8.83 (2H, br s), 7.76-7.60 (5H, m), 7.52-7.46 (2H, m), 7.30-7.05 (4H, m), 4.01 (2H, t, J = 6.6 Hz), 2.33 (3H, s), 1.85-1.54 (3H, m), 0.91 (6H, d, J = 6.6 Hz).

30 Example 19(174)

2-(3-(4-amidinophenylcarbamoyl)pyridin-4-yl)-5-((2-methylpropyl)carbamoyl) benzoic acid methanesulfonate

35 [0514]



50

55

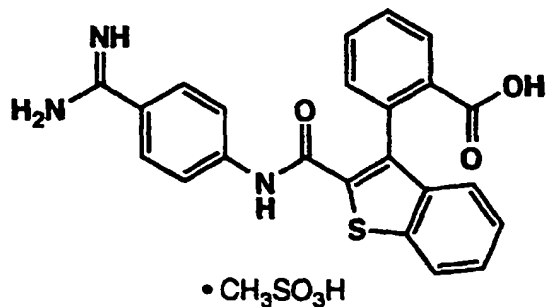
TLC : Rf 0.23 (Chloroform : Methanol : Water = 7 : 3 : 0.3) ;

NMR (d₆-DMSO) : δ 11.12 (1H, s), 9.24 (2H, brs), 9.10 (1H, s), 9.03 (2H, brs), 8.90 (1H, d, J = 5.5 Hz), 8.76 (1H, brt, J = 5.5 Hz), 8.42 (1H, d, J = 2.0 Hz), 8.08 (1H, dd, J = 8.0 Hz, 2.0 Hz), 7.77 (4H, s), 7.70 (1H, d, J = 5.5 Hz), 7.40 (1H, d, J = 8.0 Hz), 3.09 (2H, t, J = 6.0 Hz), 2.38 (3H, s), 1.95-1.75 (1H, m), 0.88 (6H, d, J = 6.5 Hz).

Example 19(175)

2-(2-(4-amidinophenylcarbamoyl)benzothiophene-3-yl)benzoic acid methanesulfonate

5 [0515]

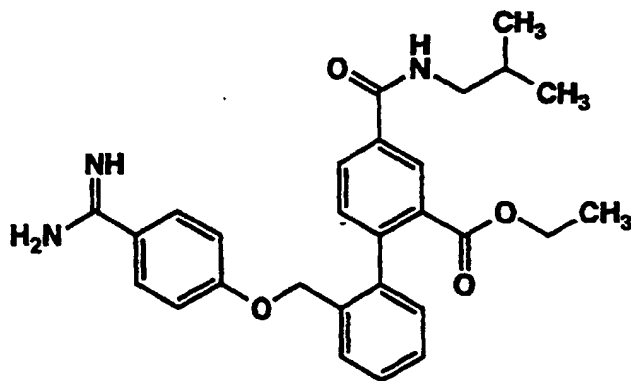
TLC : R_f 0.36 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d₆-DMSO) : δ 12.8 (1H, brs), 10.03 (1H, s), 9.17 (2H, brs), 8.89 (2H, brs), 8.13 (1H, d, J = 8.0 Hz), 7.99 (1H, dd, J = 7.5 Hz, 1.5 Hz), 7.76 (2H, d, J = 9.0 Hz), 7.69-7.48 (5H, m), 7.45-7.36 (2H, m), 7.23 (1H, d, J = 8.0 Hz), 2.34 (3H, s).

Example 19(176)

Ethyl 2'-((4-amidinophenoxy)methyl)-4-((2-methylpropyl)carbamoyl)-2-biphenylcarboxylate

[0516]

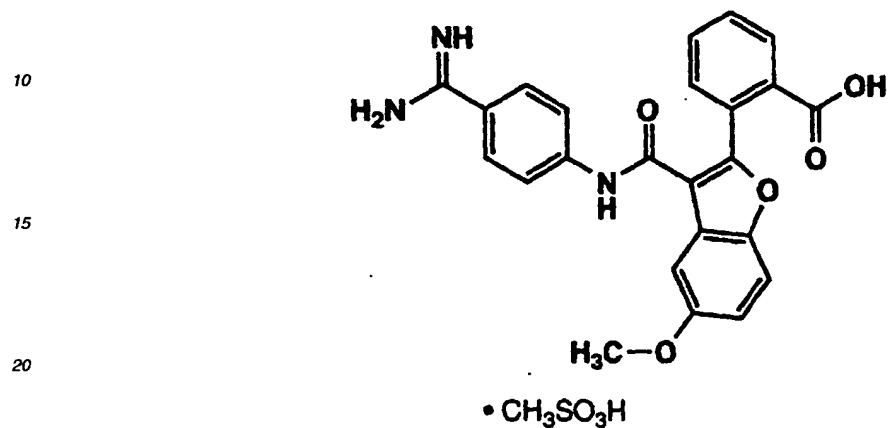
TLC : R_f 0.56 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d₆-DMSO) : δ 9.15 (2H, brs), 8.92 (2H, brs), 8.71 (1H, brt, J = 6.0 Hz), 8.31 (1H, d, J = 2.0 Hz), 8.04 (1H, dd, J = 8.0 Hz, 2.0 Hz), 7.74 (2H, d, J = 9.0 Hz), 7.59-7.53 (1H, m), 7.44 (1H, d, J = 8.0 Hz), 7.49-7.36 (2H, m), 7.17-7.12 (1H, m), 7.01 (2H, d, J = 9.0 Hz), 4.92 (1H, d, J = 12 Hz), 4.85 (1H, d, J = 12 Hz), 3.98 (2H, q, J = 7.0 Hz), 3.08 (2H, t, J = 6.0 Hz), 1.97-1.72 (1H, m), 0.88 (6H, d, J = 7.0 Hz), 0.84 (3H, t, J = 7.0 Hz).

Example 19(177)

2-(3-(4-amidinophenylcarbamoyl)-5-methoxybenzofuran-2-yl)benzoic acid methanesulfonate

5 [0517]



25

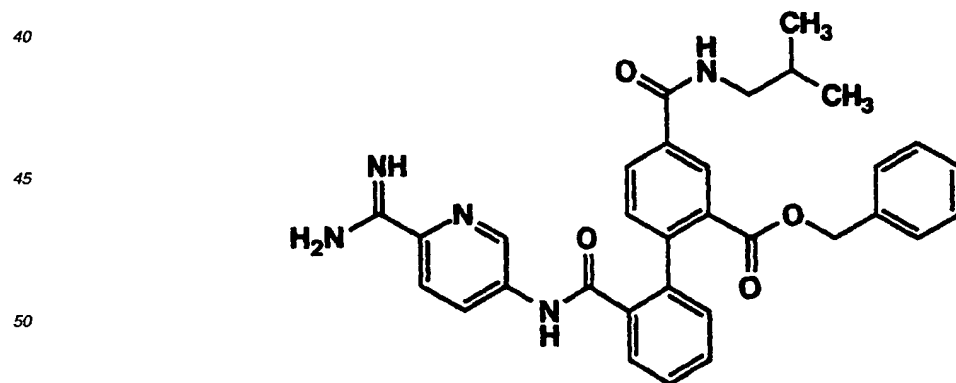
TLC : R_f 0.14 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;
 NMR (d₆-DMSO) : δ 13.2-12.8 (1H, broad), 10.48 (1H, brs), 9.17 (2H, brs), 8.89 (2H, brs), 7.91 (1H, dd, J = 7.5 Hz, 1.5 Hz), 7.83 (2H, d, J = 9.0 Hz), 7.78 (2H, d, J = 9.0 Hz), 7.74 (1H, dd, J = 7.5 Hz, 1.5 Hz), 7.70 (1H, td, J = 7.5 Hz, 1.5 Hz), 7.62 (1H, td, J = 7.5 Hz, 1.5 Hz), 7.60 (1H, d, J = 9.0 Hz), 7.26 (1H, d, J = 2.5 Hz), 7.03 (1H, dd, J = 9.0 Hz, 2.5 Hz), 3.83 (3H, s), 2.34 (3H, s).

30

Example 19(178)

35 Benzyl 2'-(6-amidinopyridin-3-ylcarbamoyl)-4-((2-methylpropyl)carbamoyl)-2-biphenylcarboxylate

[0518]



55

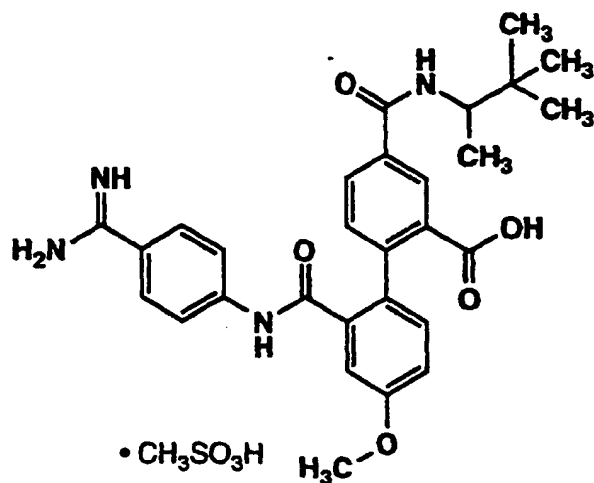
TLC : R_f 0.33 (Chloroform : Methanol : Acetic acid = 8 : 2 : 0.1) ;
 NMR (CD₃OD) : δ 8.78 (1H, d, J = 1.8 Hz), 8.33 (1H, d, J = 1.8 Hz), 8.19 (1H, dd, J = 2.6, 8.8 Hz), 8.04 (1H, s),

7.99 (1H, dd, J = 2.0, 8.0 Hz), 7.60-7.48 (2H, m), 7.44 (1H, d, J = 8.0 Hz), 7.33-7.29 (1H, m), 7.25-7.21 (3H, m), 7.14-7.09 (2H, m), 5.10 (2H, s), 3.18 (2H, d, J = 7.0 Hz), 2.02-1.81 (1H, m), 0.95 (6H, d, J = 6.6 Hz).

Example 19(179)

2'-(4-amidinophenylcarbamoyl)-4'-methoxy-4-((1, 2, 2-trimethylpropyl) carbamoyl)-2-biphenylcarboxylic acid methanesulfonate

[0519]



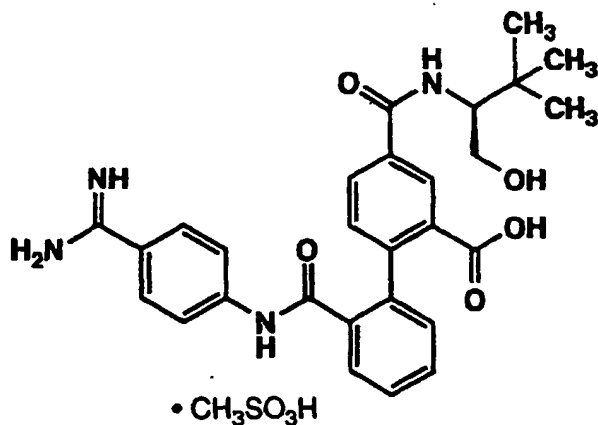
TLC : R_f 0.17 (Chloroform : Methanol : Water = 10 : 2 : 1) ;

NMR (d₆-DMSO) : δ 12.9-12.7 (1H, broad), 10.55 (1H, s), 9.17 (2H, brs), 8.91 (2H, brs), 8.23 (1H, d, J = 2.0 Hz), 8.16 (1H, d, J = 9.5 Hz), 7.92 (1H, dd, J = 8.0 Hz, 2.0 Hz), 7.73 (4H, s), 7.28 (1H, d, J = 8.0 Hz), 7.23 (1H, d, J = 2.5 Hz), 7.18 (1H, d, J = 8.5 Hz), 7.13 (1H, dd, J = 8.5 Hz, 2.5 Hz), 3.97 (1H, dq, J = 9.5 Hz, 7.0 Hz), 3.87 (3H, s), 2.33 (3H, s), 1.08 (3H, t, J = 7.0 Hz), 0.89 (9H, s).

Example 19(180)

2'-(4-amidinophenylcarbamoyl)-4-(((1S)-1-hydroxymethyl-2, 2-dimethylpropyl) carbamoyl)-2-biphenylcarboxylic acid
methanesulfonate

[0520]



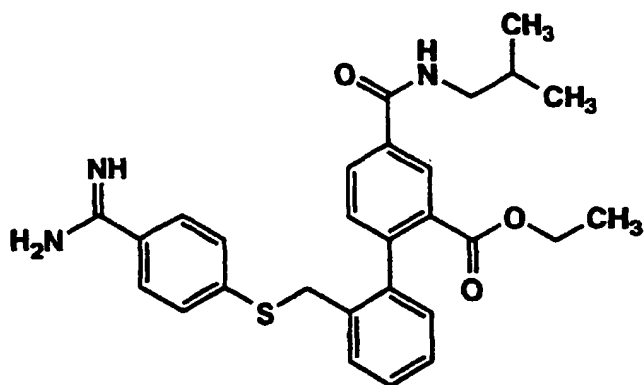
TLC : Rf 0.40 (Ethyl acetate : Acetic acid : Water = 3 : 1 : 1) ;

NMR (d₆-DMSO) : δ 10.5 (1H, s), 9.16 (2H, br s), 8.86 (2H, br s), 8.86 (1H, d, J = 1.8 Hz), 8.09 (1H, d, J = 9.6 Hz), 7.98 (1H, dd, J = 1.8, 8.0 Hz), 7.73-7.67 (5H, m), 7.67-7.52 (2H, m), 7.31 (1H, d, J = 8.0 Hz), 7.28-7.24 (1H, m), 4.40 (1H, br s), 3.96-3.82 (1H, m), 3.70-3.62 (1H, m), 3.51-3.41 (1H, m), 2.33 (3H, s), 0.88 (9H, s).

Example 19(181)

Ethyl 2'-(4-amidinophenylthiomethyl)-4-((2-methylpropyl)carbamoyl)-2-biphenylcarboxylate

[0521]



TLC : Rf 0.67 (Chloroform : Methanol : Water = 7 : 3 : 0.3) ;

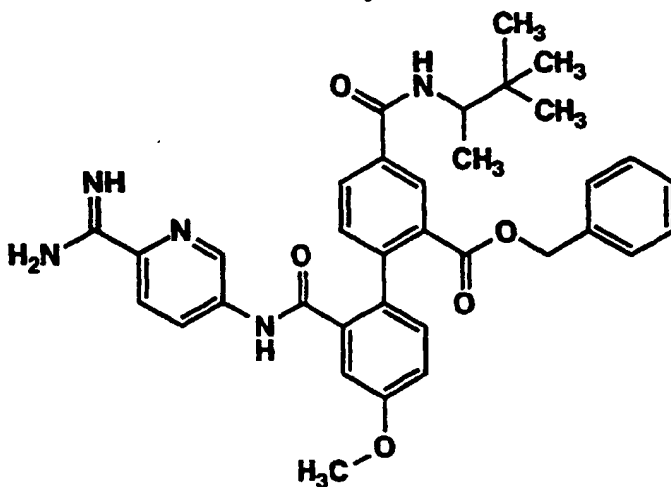
NMR (d₆-DMSO) : δ 9.25 (2H, s), 8.97 (2H, s), 8.73 (1H, br t, J = 6.6 Hz), 8.37 (1H, d, J = 1.8 Hz), 8.08 (1H, dd, J

= 1.8, 8.0 Hz), 7.67 (2H, d, J = 8.8 Hz), 7.53 (1H, m), 7.45 (1H, d, J = 8.0 Hz), 7.30-7.38 (4H, m), 7.10 (1H, m), 4.13 (1H, d, J = 13.0 Hz), 4.04 (1H, d, J = 13.0 Hz), 4.02 (2H, q, J = 7.2 Hz), 3.12 (2H, t, J = 6.6 Hz), 1.87 (1H, m), 0.91 (6H, d, J = 6.6 Hz), 0.89 (3H, t, J = 7.2 Hz).

5 Example 19(182)

Benzyl 2'-(6-amidinopyridin-3-ylcarbamoyl)-2-((1, 2, 2-trimethylpropyl) carbamoyl)-2-biphenylcarboxylate

[0522]



TLC : Rf 0.67 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (CD₃OD) : δ 8.77 (1H, d, J = 2.5 Hz), 8.25 (1H, d, J = 2.0 Hz), 8.18 (1H, dd, J = 8.5 Hz, 2.5 Hz), 8.02 (1H, d, J = 8.5 Hz), 7.93 (1H, dd, J = 8.0 Hz, 2.0 Hz), 7.42 (1H, d, J = 8.0 Hz); 7.27-7.17 (5H, m), 7.26-7.09 (2H, m), 7.08 (1H, dd, J = 8.5 Hz, 2.5 Hz), 5.10 (2H, s), 4.05 (1H, q, J = 7.0 Hz), 3.89 (3H, s), 1.15 (3H, d, J = 7.0 Hz), 0.95 (9H, s).

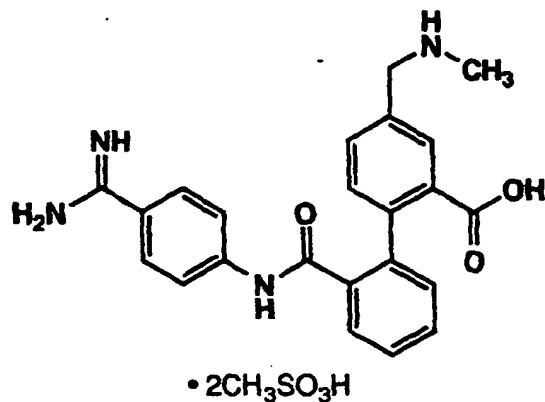
Example 20 — Example 20(20)

[0523] The following compounds were obtained by the same procedure as a series of reaction of Example 4, Example 2, Example 11 or Reference Example 8, using a compound prepared in Example 19(86) - Example 19(94), Example 19(55), Example 19(95), Example 19(105), Example 19(133) — Example 19(136), Example 19(158), Example 19(176); Example 19(178) and Example 19(181) — Example 19(182).

Example 20

2'-(4-amidinophenylcarbamoyl)-4-methylaminomethyl-2-biphenylcarboxylic acid dimethanesulfonate

5 [0524]



25

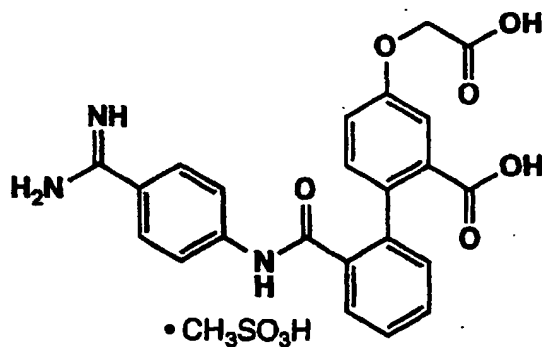
TLC : Rf 0.29 (Ethyl acetate : Acetic acid : Water = 3 : 1 : 1) ;
 NMR (d₆-DMSO) : δ 10.55 (1H, s), 9.15 (2H, s), 8.92 (2H, s), 8.85 (2H, br.s), 8.01 (1H, d, J = 1.8 Hz), 7.75 (4H, s),
 7.70 (1H, dd, J = 1.8, 7.8 Hz), 7.62 (1H, dd, J = 1.8, 8.0 Hz), 7.52-7.58 (2H, m), 7.32 (1H, d, J = 8.0 Hz), 7.25 (1H,
 dd, J = 1.8, 7.8 Hz), 4.20 (2H, t, J = 5.6 Hz), 2.57 (3H, t, J = 5.6 Hz), 2.37 (6H, s).

30

Example 20(1)

2'-(4-amidinophenylcarbamoyl)-4-carboxymethoxy-2-biphenylcarboxylic acid methanesulfonate

35 [0525]



40

45

50

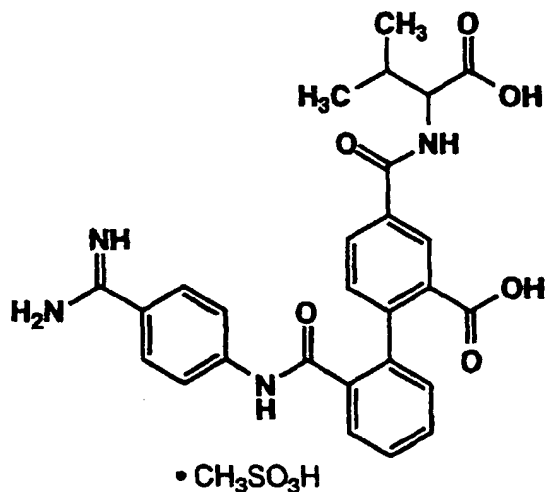
TLC : Rf 0.45 (Ethyl acetate : Acetic acid : Water = 6 : 1 : 0.5) ;
 NMR (d₆-DMSO) : δ 13.4-12.5 (2H, br), 10.41 (1H, s), 9.20 (2H, br.s), 8.97 (2H, br.s), 7.76 (2H, d, J = 8.8 Hz), 7.69
 (2H, d, J = 8.8 Hz), 7.7-7.6 (1H, m), 7.6-7.4 (2H, m), 7.28 (1H, d, J = 2.8 Hz), 7.3-7.1 (2H, m), 7.06 (1H, dd, J = 8.8,
 2.8 Hz), 4.72 (2H, s), 2.31 (3H, s).

55

Example 20(2)

2'-(4-amidinophenylcarbamoyl)-4-((1-carboxy-2-methylpropyl)carbamoyl)-2-biphenylcarboxylic acid methanesulfonate

5 [0526]

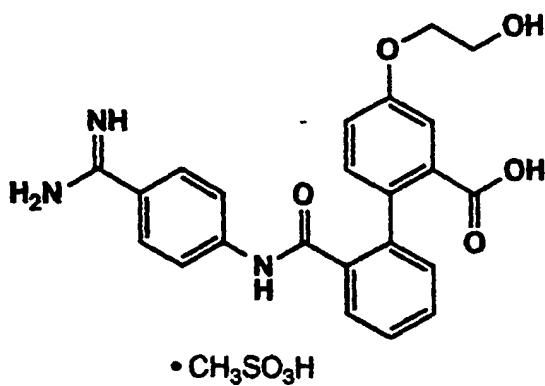
TLC : R_f 0.12 (Chloroform : Methanol : Water = 7 : 3 : 0.3) ;

NMR (d₆-DMSO) : δ 10.57 (1H, s), 9.24 (2H, s), 9.04 (2H, s), 8.68 (1H, d, J = 7.8 Hz), 8.34 (1H, s), 8.02 (1H, d, J = 7.8 Hz), 7.76 (5H, br.s), 7.52-7.60 (2H, m), 7.26-7.36 (2H, m), 4.31 (1H, t, J = 7.0 Hz), 2.37 (3H, s), 2.19 (1H, m), 0.99 (3H, d, J = 6.0 Hz), 0.97 (3H, d, J = 6.0 Hz).

Example 20(3)

2'-(4-amidinophenylcarbamoyl)-4-(2-hydroxyethoxy)-2-biphenylcarboxylic acid methanesulfonate

[0527]



EP 1 078 917 A1

TLC : Rf 0.22 (Chloroform : Methanol : Water = 10 : 3 : 0.2) ;

NMR (d_6 -DMSO) : δ 13.1-12.0 (1H, br), 10.36 (1H, s), 9.13 (2H, br.s), 8.78 (2H, br.s), 7.8-7.5 (5H, m), 7.6-7.4 (2H, m), 7.4-7.0 (4H, m), 4.00 (2H, t, J = 4.8 Hz), 3.69 (2H, t, J = 4.8 Hz), 3.6-3.2 (1H, br), 2.31 (3H, s).

5 Example 20(4)

3-(2-(4-amidinophenylcarbamoyl)phenyl)-5-hydroxy-2-naphthalenecarboxylic acid methanesulfonate

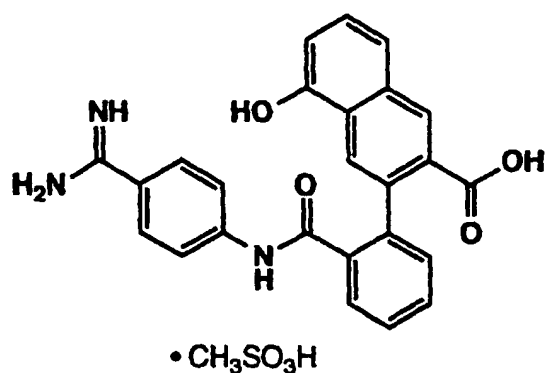
[0528]

10

15

20

25



TLC : Rf 0.23 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

30 NMR (d_6 -DMSO) : δ 13.0-12.2 (1H, br), 10.45 (1H, s), 10.31 (1H, br.s), 9.09 (2H, br.s), 8.75 (2H, br.s), 8.35 (1H, s), 7.91 (1H, s), 7.75-7.3 (10H, m), 6.94 (1H, d, J = 7.4 Hz), 2.31 (3H, s).

Example 20(5)

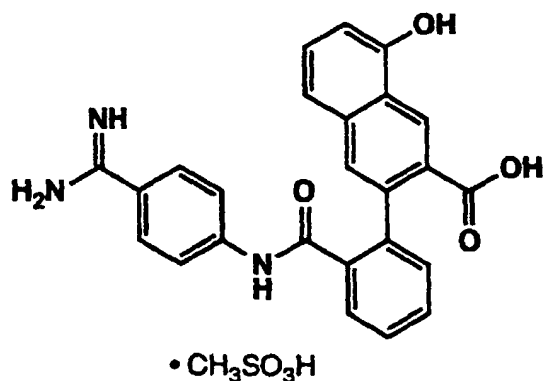
35 3-(2-(4-amidinophenylcarbamoyl)phenyl)-8-hydroxy-2-naphthalenecarboxylic acid methanesulfonate

[0529]

40

45

50



55

TLC : Rf 0.34 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

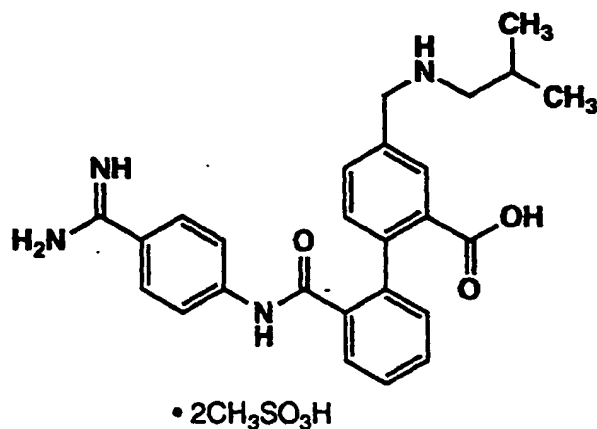
NMR (d_6 -DMSO) : δ 13.2-12.0 (1H, br), 10.6-10.4 (1H, br), 10.43 (1H, s), 9.12 (2H, brs), 8.85 (2H, brs), 8.66 (1H,

s), 7.8-7.5 (8H, m), 7.5-7.3 (3H, m), 6.92 (1H, d, J = 6.4 Hz), 2.32 (3H, s).

Example 20(6)

5 2'-(4-amidinophenylcarbamoyl)-4-((2-methylpropyl)aminomethyl)-2-biphenylcarboxylic acid dimethanesulfonate

[0530]



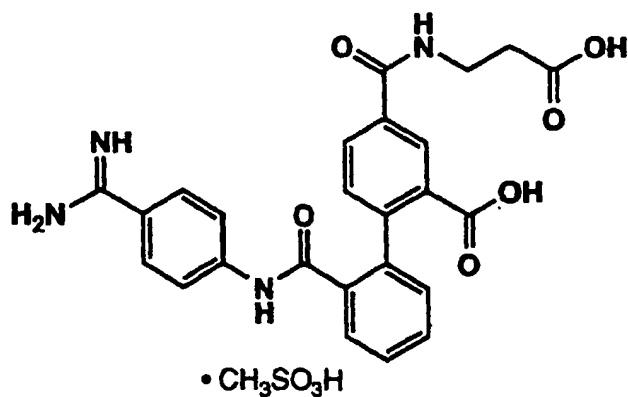
TLC : Rf 0.16 (Chloroform : Methanol : Water = 8 : 2 : 0.1) ;

NMR (d₆-DMSO) : δ 10.6 (1H, s), 9.16 (2H, br s), 8.94 (2H, br s), 8.75 (2H, br s), 8.05 (1H, s), 7.80-7.60 (6H, m), 7.60-7.50 (2H, m), 7.34-7.23 (2H, m), 4.22 (2H, br s), 2.79 (2H, br s), 2.39 (3H, s), 2.37 (3H, s), 2.06-1.93 (1H, m), 0.94 (6H, d, J = 6.6 Hz).

Example 20(7)

35 2'-(4-amidinophenylcarbamoyl)-4-((2-carboxyethyl)carbamoyl)-2-biphenylcarboxylic acid methanesulfonate

[0531]



EP 1 078 917 A1

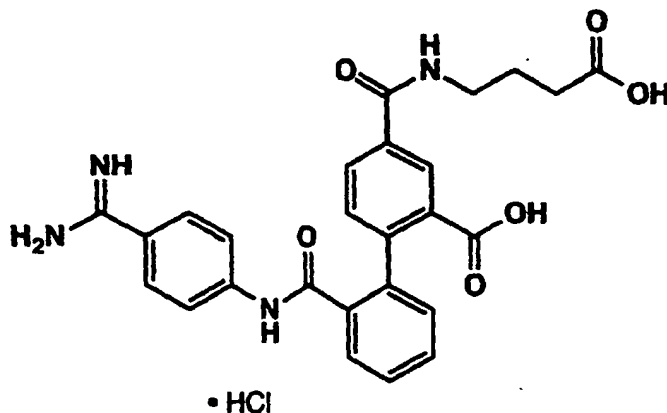
TLC : Rf 0.60 (Ethyl acetate : Acetic acid : Water = 3 : 1 : 1) ;

NMR (d₆-DMSO) : δ 13.0-12.0 (2H, broad), 10.53 (1H, s), 9.18 (2H, brs), 8.92 (2H, brs), 8.74 (1H, brt, J = 5.5 Hz), 8.29 (1H, d, J = 2.0 Hz), 7.95 (1H, dd, J = 8.0 Hz, 2.0 Hz), 7.28 (4H, s), 7.70 (1H, dd, J = 7.5 Hz, 2.0 Hz), 7.62-7.47 (2H, m), 7.32 (1H, d, J = 8.0 Hz), 7.27 (1H, dd, J = 7.5 Hz, 2.0 Hz), 3.45 (2H, q, J = 7.0 Hz), 2.51 (2H, t, J = 7.0 Hz), 2.34 (3H, s).

Example 20(8)

2'-(4-amidinophenylcarbamoyl)-4-((3-carboxypropyl)carbamoyl)-2-biphenylcarboxylic acid hydrochloride

[0532]



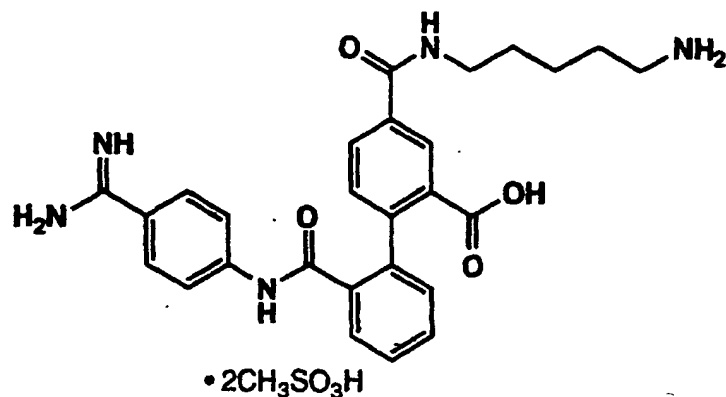
TLC : Rf 0.65 (Ethyl acetate : Acetic acid : Water = 3 : 1 : 1) ;

NMR (d₆-DMSO) : δ 12.8-12.1 (2H, broad), 10.57 (1H, s), 9.25 (2H, brs), 9.04 (2H, brs), 8.71 (1H, brt, J = 6.0 Hz), 8.30 (1H, d, J = 2.0 Hz), 7.97 (1H, dd, J = 7.5 Hz, 2.0 Hz), 7.77 (2H, d, J = 9.0 Hz), 7.71 (2H, d, J = 9.0 Hz), 7.70 (1H, dd, J = 7.5 Hz, 2.0 Hz), 7.62-7.47 (2H, m), 7.31 (1H, d, J = 8.0 Hz), 7.26 (1H, dd, J = 7.5 Hz, 2.0 Hz), 3.27 (2H, q, J = 6.0 Hz), 2.27 (2H, t, J = 7.0 Hz), 1.74 (2H, quint, J = 7.0 Hz).

Example 20(9)

2'-(4-amidinophenylcarbamoyl)-4-((5-aminopentyl)carbamoyl)-2-biphenylcarboxylic acid dimethanesulfonate

5 [0533]



25

TLC : R_f 0.11 (Ethyl acetate : Acetic acid : Water = 3 : 1 : 1) ;

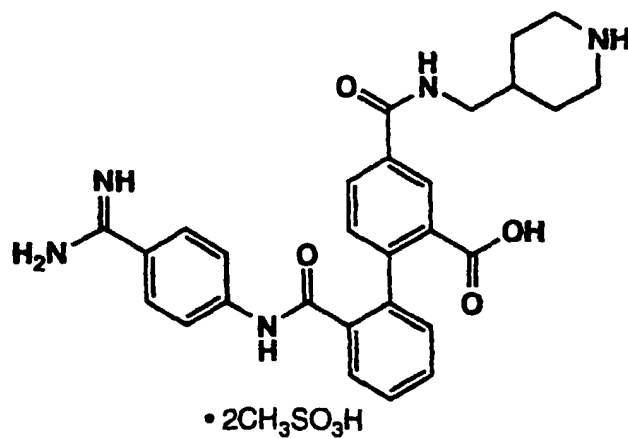
NMR (d₆-DMSO) : δ 10.6 (1H, s), 9.15 (2H, br s), 8.90 (2H, br s), 8.66 (1H, t, J = 5.6 Hz), 8.31 (1H, d, J = 1.8 Hz), 7.98 (1H, dd, J = 1.8, 8.0 Hz), 7.81-7.35 (7H, m), 7.35-7.26 (2H, m), 4.20 (3H, br s), 3.28 (2H, q, J = 6.2 Hz), 2.79 (2H, q, J = 7.4 Hz), 2.37 (3H, s), 2.36 (3H, s), 1.70-1.20 (6H, m).

30

Example 20(10)

2'-(4-amidinophenylcarbamoyl)-4-((piperidin-4-ylmethyl)carbamoyl)-2-biphenylcarboxylic acid dimethanesulfonate

35 [0534]



55

TLC : R_f 0.16 (Ethyl acetate : Acetic acid : Water = 3 : 1 : 1) ;

NMR (d₆-DMSO) : δ 10.6 (1H, s), 9.17 (2H, br s), 8.95 (2H, br s), 8.78 (1H, t, J = 6.0 Hz), 8.58-8.55 (1H, m), 8.32

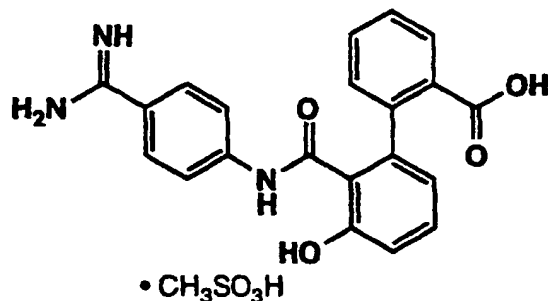
EP 1 078 917 A1

(1H, d, J = 1.8 Hz), 8.25-8.21 (1H, m), 7.99 (1H, dd, J = 1.8, 7.8 Hz), 7.78-7.70 (5H, m), 7.60-7.53 (2H, m), 7.35-7.27 (2H, m), 3.29-3.17 (4H, m), 2.89-2.79 (2H, m), 2.39 (6H, s), 1.84-1.80 (3H, m), 1.42-1.30 (2H, m).

Example 20(11)

2'-(4-amidinophenylcarbamoyl)-3'-hydroxy-2-biphenylcarboxylic acid methanesulfonate

[0535]

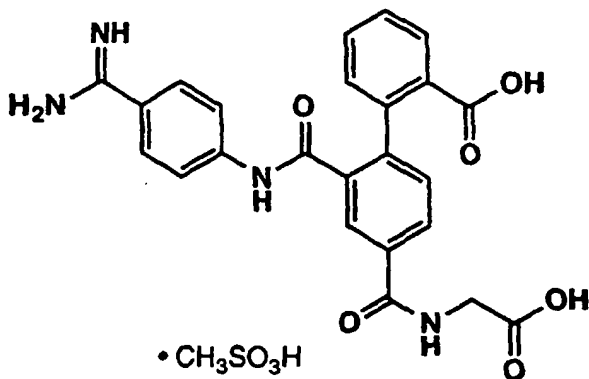


TLC : Rf 0.27 (Chloroform : Methanol : Water = 7 : 3 : 0.3) ;
NMR (d_6 -DMSO) : δ 13.0-12.0 (1H, broad), 10.34 (1H, s), 10.20-9.85 (1H, broad), 9.13 (2H, brs), 8.94 (2H, brs), 7.76 (1H, d, J = 7 Hz), 7.72 (2H, d, J = 9 Hz), 7.63 (2H, d, J = 9 Hz), 7.50-7.18 (4H, m), 6.95 (1H, d, J = 8 Hz), 6.63 (1H, d, J = 8 Hz), 2.41 (3H, s).

Example 20(12)

2'-(4-amidinophenylcarbamoyl)-4'-((carboxymethyl)carbamoyl)-2-biphenylcarboxylic acid methanesulfonate

[0536]



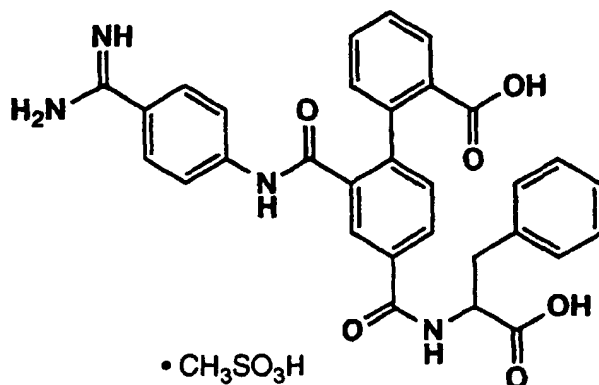
TLC : Rf 0.56 (Ethyl acetate : Acetic acid : Water = 3 : 1 : 1) ;
NMR (d_6 -DMSO) : δ 10.60 (1H, s), 9.15 (2H, s), 9.03 (1H, br.t, J = 5.4 Hz), 8.81 (2H, s), 8.17 (1H, d, J = 1.6 Hz), 8.03 (1H, dd, J = 1.8, 8.0 Hz), 7.87 (1H, dd, J = 1.6, 7.8 Hz), 7.75 (2H, d, J = 9.2 Hz), 7.70 (2H, d, J = 9.2 Hz), 7.55

(1H, dd, J = 1.8, 8.0 Hz), 7.44 (1H, dt, J = 1.8, 8.0 Hz), 7.39 (1H, d, J = 7.8 Hz), 7.27 (1H, dd, J = 1.8, 8.0 Hz), 3.99 (2H, br.d, J = 5.4 Hz), 2.34 (3H, s).

Example 20(13)

2'-(4-amidinophenylcarbamoyl)-4'-((1-carboxy-2-phenylethyl)carbamoyl)-2-biphenylcarboxylic acid methanesulfonate

[0537]



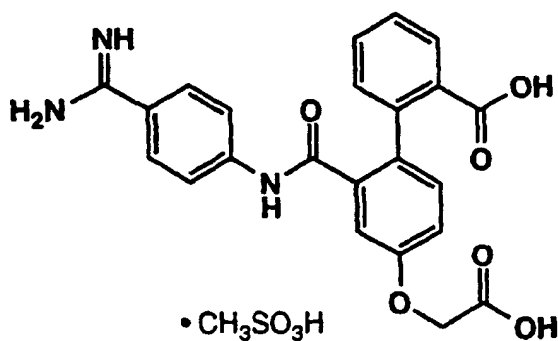
TLC : Rf 0.76 (Ethyl acetate : Acetic acid : Water = 3 : 1 : 1) ;

NMR (d₆-DMSO) : δ 10.57 (1H, s), 9.16 (2H, s), 8.92 (1H, br.d, J = 5.4 Hz), 8.87 (2H, s), 8.09 (1H, s), 7.97 (1H, d, J = 7.8 Hz), 7.87 (1H, d, J = 7.8 Hz), 7.75 (2H, d, J = 9.2 Hz), 7.70 (2H, d, J = 9.2 Hz), 7.55 (1H, t, J = 7.8 Hz), 7.44 (1H, t, J = 7.8 Hz), 7.19-7.38 (7H, m), 4.70 (1H, m), 3.04-3.29 (2H, m), 2.35 (3H, s).

Example 20(14)

2'-(4-amidinophenylcarbamoyl)-4'-carboxymethoxy-2-biphenylcarboxylic acid methanesulfonate

[0538]



TLC : Rf 0.44 (Ethyl acetate : Acetic acid : Water = 6 : 1 : 0.5) ;

NMR (d₆-DMSO) : δ 10.37 (1H, s), 9.14 (2H, br.s), 8.84 (2H, br.s), 7.8-7.6 (5H, m), 7.49 (1H, t, J = 6.8 Hz), 7.37

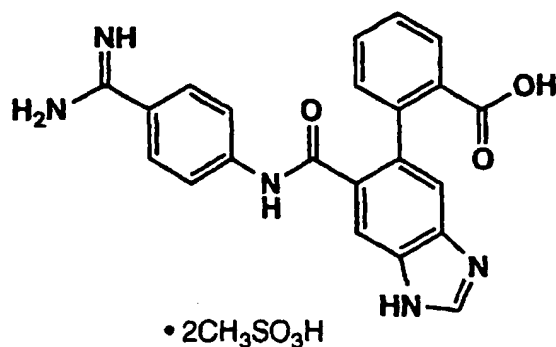
EP 1 078 917 A1

(1H, t, J = 6.8 Hz), 7.3-7.0 (4H, m), 4.79 (2H, s), 4.4-2.8 (2H, br), 2.35 (3H, s).

Example 20(15)

2-(6-(4-amidinophenylcarbamoyl)benzimidazol-5-yl)benzoic acid dimethanesulfonate

[0539]



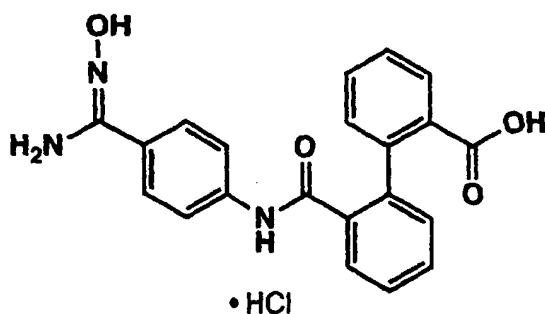
TLC : Rf 0.16 (Chloroform : Methanol : Water = 7 : 3 : 03) ;

NMR (d₆-DMSO) : δ 10.57 (1H, s), 9.37 (1H, s), 9.17 (2H, s), 8.82 (2H, s), 8.10 (1H, s), 7.86 (1H, d, J = 7.8 Hz), 7.75 (2H, d, J = 9.0 Hz), 7.68 (2H, d, J = 9.0 Hz), 7.63 (1H, s), 7.56 (1H, t, J = 7.8 Hz), 7.44 (1H, t, J = 7.8 Hz), 7.30 (1H, d, J = 7.8 Hz), 2.35 (6H, s).

Example 20(16)

2'-(4-(N²-hydroxyamidino)phenylcarbamoyl)-2-biphenylcarboxylic acid hydrochloride

[0540]



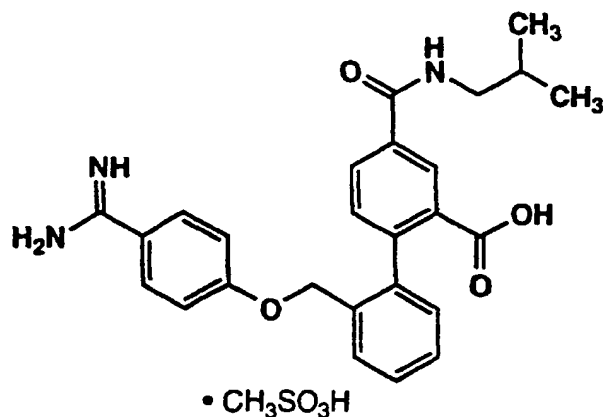
TLC : Rf 0.31 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d₆-DMSO) : δ 10.47 (1H, s), 8.92 (2H, brs), 7.80 (1H, dd, J = 1.0, 8.0 Hz), 7.70-7.30 (9H, m), 7.28-7.18 (2H, m), 3.80-3.00 (2H, m).

Example 20(17)

2'-(4-amidinophenoxy)methyl)-4-((2-methylpropyl)carbamoyl)-2-biphenylcarboxylic acid methanesulfonate

[0541]



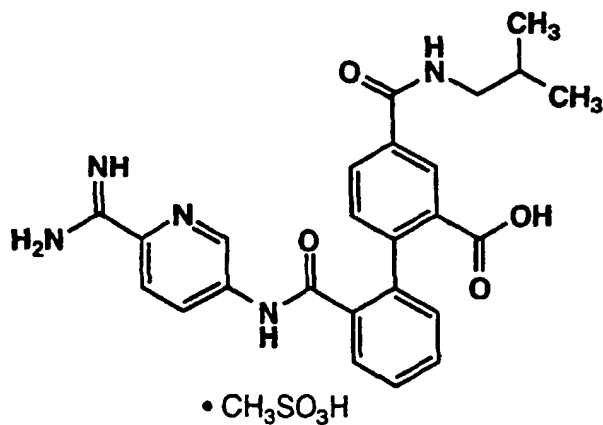
TLC : Rf 0.43 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d₆-DMSO) : δ 13.0-12.7 (1H, broad), 9.08 (2H, brs), 8.84 (2H, brs), 8.67 (1H, brt, J = 6.0 Hz), 8.33 (1H, d, J = 2.0 Hz), 7.98 (1H, dd, J = 8.0 Hz, 2.0 Hz), 7.70 (2H, d, J = 9.0 Hz), 7.54-7.48 (1H, m), 7.39 (1H, d, J = 8.0 Hz), 7.44-7.33 (2H, m), 7.18-7.12 (1H, m), 7.04 (2H, d, J = 9.0 Hz), 4.92 (2H, s), 3.08 (2H, t, J = 6.0 Hz), 2.31 (3H, s), 1.95-1.75 (1H, m), 0.88 (6H, d, J = 7.0 Hz).

Example 20(18)

2'-(6-amidinopyridin-3-ylcarbamoyl)-4-((2-methylpropyl)carbamoyl)-2-biphenylcarboxylic acid methanesulfonate

[0542]



TLC : Rf 0.51 (Chloroform : Methanol : Water = 7 : 3 : 0.3) ;

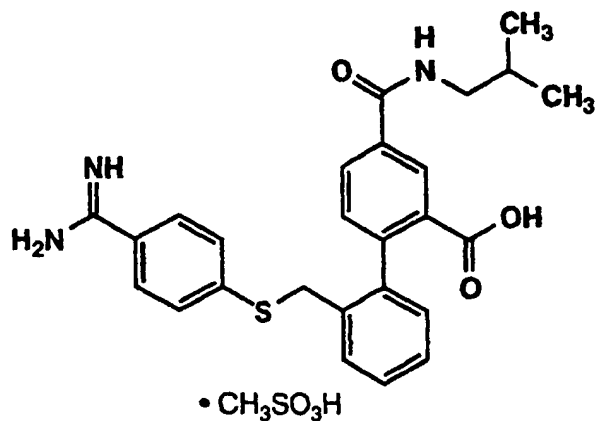
NMR (d₆-DMSO) : δ 10.9 (1H, s), 9.38 (2H, br s), 9.12 (2H, br s), 8.90 (1H, d, J = 2.2 Hz), 8.66 (1H, t, J = 6.0 Hz),

8.29 (1H, d, J = 1.8 Hz), 8.26-8.16 (2H, m), 7.98 (1H, dd, J = 1.8, 8.0 Hz), 7.75 (1H, dd, J = 1.8, 7.0 Hz), 7.68-7.52 (2H, m), 7.35-7.28 (2H, m), 3.08 (1H, t, J = 6.2 Hz), 2.34 (3H, s), 1.91-1.77 (1H, m), 0.88 (6H, d, J = 6.6 Hz).

Example 20(19)

2'-(4-amidinophenylthiomethyl)-4-((2-methylpropyl)carbamoyl)-2-biphenylcarboxylic acid methanesulfonate

[0543]



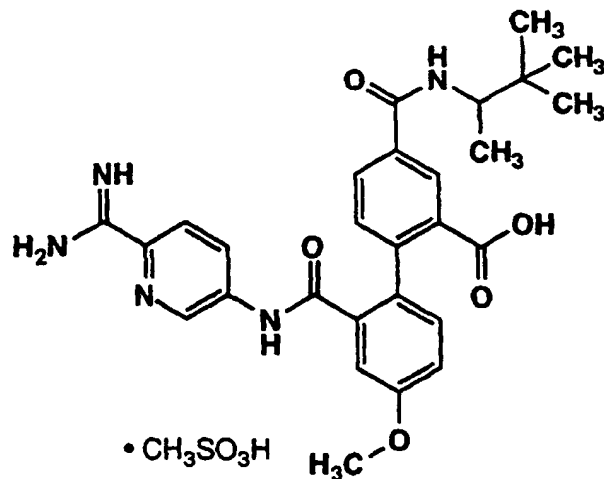
TLC : R_f 0.47 (Chloroform : Methanol : Water = 7 : 3 : 0.3) ;

NMR (d₆-DMSO) : δ 9.18 (2H, s), 8.89 (2H, s), 8.70 (1H, br.t, J = 6.3 Hz), 8.38 (1H, s), 8.03 (1H, d, J = 8.0 Hz), 7.64 (2H, d, J = 8.8 Hz), 7.52 (1H, d, J = 8.0 Hz), 7.40 (1H, d, J = 8.0 Hz), 7.30-7.38 (4H, m), 7.11 (1H, d, J = 8.0 Hz), 4.17 (1H, d, J = 13.6 Hz), 4.02 (1H, d, J = 13.6 Hz), 3.11 (2H, t, J = 6.3 Hz), 2.36 (3H, s), 1.87 (1H, m), 0.90 (6H, d, J = 6.3 Hz).

Example 20(20)

2'-(6-amidinopyridin-3-ylcarbamoyl)-4'-methoxy-4-((1, 2, 2-trimethylpropyl) carbamoyl)-2-biphenylcarboxylic acid methanesulfonate

[0544]



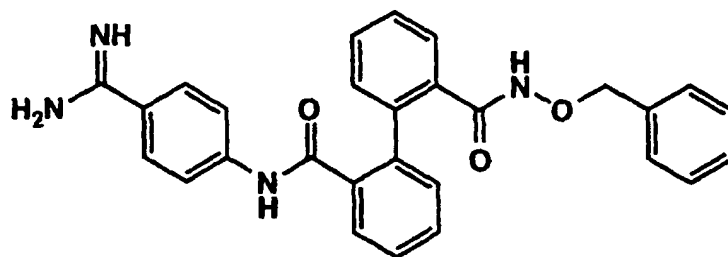
TLC : R_f 0.19 (Chloroform : Methanol : Water = 10 : 2 : 1) ;

NMR (d₆-DMSO) : δ 13.0-12.0 (1H, broad), 10.88 (1H, s), 9.36 (2H, brs), 9.10 (2H, brs), 8.91 (1H, d, J = 2.5 Hz), 8.27 (1H, dd, J = 9.0 Hz, 2.5 Hz), 8.23 (1H, d, J = 2.0 Hz), 8.17 (1H, d, J = 9.0 Hz), 8.15 (1H, d, J = 9.0 Hz), 7.94 (1H, dd, J = 8.0 Hz, 2.0 Hz), 7.30 (1H, d, J = 8.0 Hz), 7.29 (1H, d, J = 2.0 Hz), 7.22 (1H, d, J = 8.5 Hz), 7.16 (1H, dd, J = 8.5 Hz, 2.0 Hz), 3.98 (1H, dq, J = 9.0 Hz, 7.0 Hz), 3.88 (3H, s), 2.34 (3H, s), 1.07 (3H, d, J = 7.0 Hz), 0.89 (9H, s).

Example 21

N-benzyloxy-2'-(4-amidinophenylcarbamoyl)-2-biphenylcarboxamide

[0545]



[0546] The compound prepared in Example 19(1) (147 mg) and O-benzylhydroxyamine hydrochloride (178 mg) were dissolved into dimethylformamide (1 ml) and pyridine (1 ml). Dicyclohexylcarbodiimide (115 mg) was added to the mixture. The mixture was stirred for 18 hours at room temperature. The reaction mixture was filtered, and the solid was

washed with dimethylformamide. The solution of washings and filtrate was concentrated. The residue was purified by column chromatography on silica gel (Chloroform : Methanol : Water = 9 : 1 : 0.1 → 8 : 2 : 0.1) to give the present compound having the following physical data.

- 5 TLC : Rf 0.40 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;
 NMR (d₆-DMSO) : δ 10.88 (1H, brs), 9.40-8.70 (3H, broad), 7.75-7.63 (3H, m), 7.60-7.46 (4H, m), 7.46-7.32 (8H, m), 7.18-7.10 (2H, m), 4.73 (2H, s).

Example 21(1) - Example 21(10)

- 10 [0547] The following compounds were obtained by the same procedure as a series of reaction of Example 21, using
 a compound prepared in Example 19(1), Example 19(41), Example 19(47) — Example 19(48), Example 6, Example
 19(100), Example 4, Example 19(112), Example 19(159) and Example 19(1), subject to using N-methyl-O-benzylhy-
 15 droxyamine instead of O-benzylhydroxyamine in Example 21(1), and using cyanamide instead of O-benzylhy-
 droxyamine in Example 21(10).

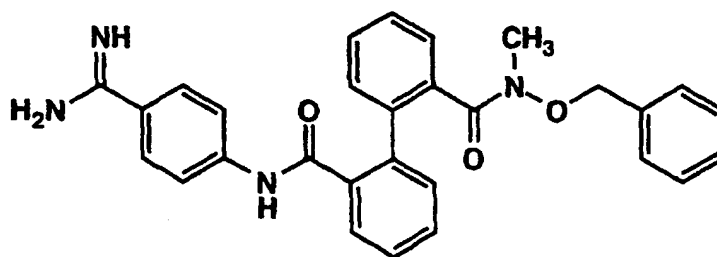
Example 21(1)

N-benzyloxy-N-methyl-2'-(4-amidinophenylcarbamoyl)-2-biphenyl carboxamide

20

[0548]

25



30

35

TLC : Rf 0.24 (Chloroform : Methanol : Acetic acid = 20 : 2 : 1) ;
 NMR (d₆-DMSO) : δ 10.9-10.3 (1H, broad), 9.17 (3H, brs), 7.76-7.00 (17H, m), 4.84 (2H, brs), 3.17 (3H, brs).

40

45

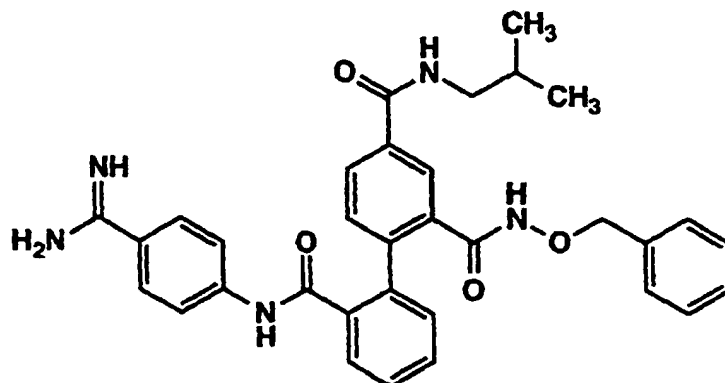
50

55

Example 21(2)

N-benzyloxy-2'-(4-amidinophenylcarbamoyl)-4-((2-methylpropyl)carbamoyl)-2-biphenylcarboxamide

5 [0549]



25

TLC : Rf 0.31 (Chloroform : Methanol : Water = 8 : 2 : 0.2) ;

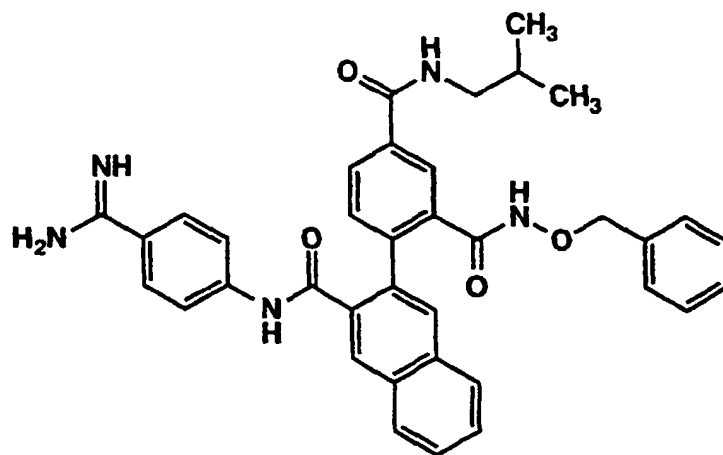
NMR (d₆-DMSO) : δ 10.92 (1H, br.s), 9.08 (3H, br.s), 8.63 (1H, br.t, J = 6.6 Hz), 8.01 (1H, d, J = 1.8 Hz), 7.90 (1H, dd, J = 1.8, 8.0 Hz), 7.69-7.76 (3H, m), 7.55-7.62 (4H, m), 7.37 (5H, s), 7.26 (1H, d, J = 8.0 Hz), 7.16 (1H, m), 4.75 (2H, s), 3.07 (2H, t, J = 6.6 Hz), 1.84 (1H, m), 0.88 (6H, d, J = 6.6 Hz).

30

Example 21(3)

N-benzyloxy-2-(3-(4-amidinophenylcarbamoyl)naphthalen-2-yl)-5-((2-methylpropyl)carbamoyl)benzcarboxamide

35 [0550]



50

55

TLC : Rf 0.28 (Chloroform : Methanol : Water = 8 : 2 : 0.2) ;

EP 1 078 917 A1

NMR (CD₃OD) : δ 8.24 (1H, s), 8.06 (1H, m), 8.00 (1H, d, J = 1.8 Hz), 7.94 (1H, m), 7.87 (1H, dd, J = 1.8, 8.0 Hz), 7.64-7.70 (7H, m), 7.35 (1H, d, J = 8.0 Hz), 7.16-7.29 (5H, m), 4.65 (2H, br.s), 3.18 (2H, d, J = 7.0 Hz), 1.91 (1H, m), 0.95 (6H, d, J = 6.6 Hz).

5 Example 21(4)

N-benzyloxy-2'-(4-amidinophenylcarbamoyl)-4'-methoxy-4-((2-methylpropyl) carbamoyl)-2-biphenylcarboxamide

[0551]

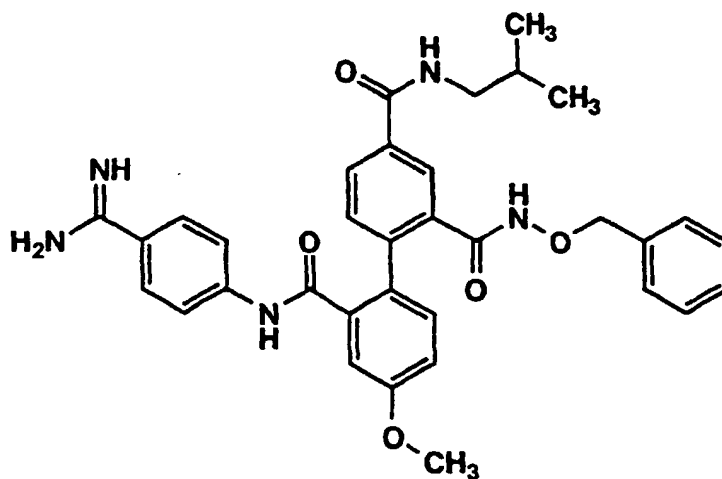
10

15

20

25

30



35

40

TLC : Rf 0.28 (Chloroform : Methanol : Water = 8 : 2 : 0.2) ;

NMR (CD₃OD) : δ 7.93 (1H, d, J = 1.8 Hz), 7.82 (1H, dd, J = 1.8, 8.0 Hz), 7.68 (2H, d, J = 9.2 Hz), 7.61 (2H, d, J = 9.2 Hz), 7.39 (5H, s), 7.26 (1H, d, J = 8.0 Hz), 7.22 (1H, t, J = 1.4 Hz), 7.10 (2H, d, J = 1.4 Hz), 4.84 (2H, s), 3.90 (3H, s), 3.16 (2H, d, J = 7.4 Hz), 1.89 (1H, m), 0.94 (6H, d, J = 6.6 Hz).

Example 21(5)

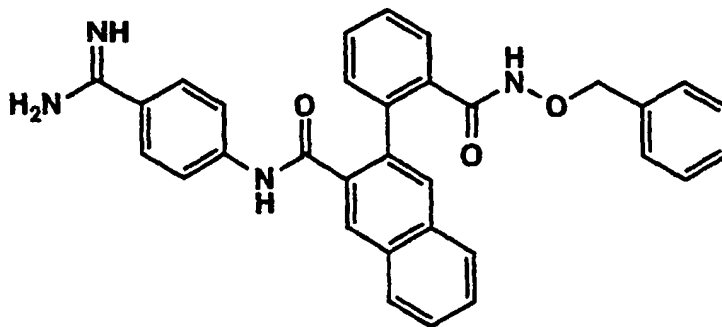
40 N-benzyloxy-2-(3-(4-amidinophenylcarbamoyl)naphthalen-2-yl) benzcarboxamide

[0552]

45

50

55



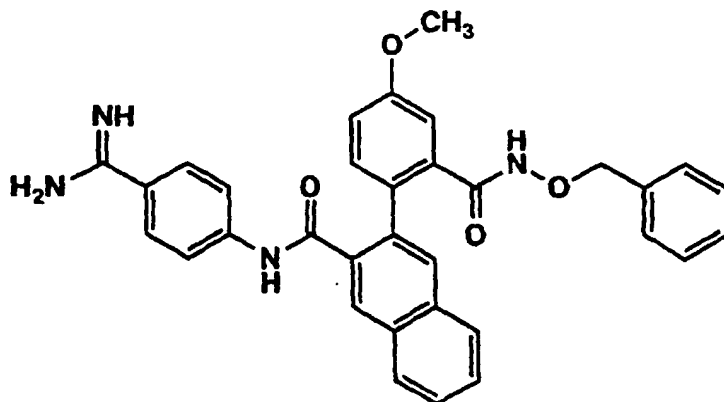
TLC : Rf 0.48 (Chloroform : Methanol : Water = 10 : 3 : 0.2) ;

NMR (d₆-DMSO) : δ 11.21 (1H, br), 9.11 (3H, br), 8.29 (1H, s), 8.11 (1H, m), 7.95 (1H, m), 7.8-7.5 (7H, m), 7.6-7.3 (4H, m), 7.4-7.1 (6H, m), 4.63 (2H, s).

Example 21(6)

N-benzyloxy-2-(3-(4-amidinophenylcarbamoyl)naphthalen-2-yl)-5-methoxy benzcarboxamide

[0553]



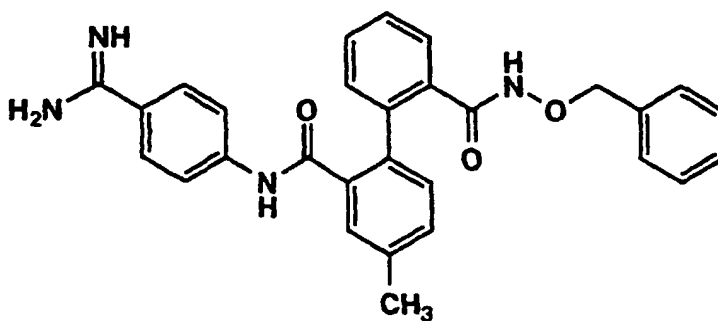
TLC : Rf 0.39 (Chloroform : Methanol : Water = 10 : 3 : 0.2) ;

NMR (d₆-DMSO) : δ 11.87 (1H, s), 11.04 (1H, s), 9.3-9.0 (3H, s), 8.27 (1H, s), 8.10 (1H, m), 7.96 (1H, m), 7.78 (2H, d, J = 9.4 Hz), 7.8-7.5 (4H, m), 7.5-7.1 (7H, m), 7.1-6.9 (2H, m), 4.64 (2H, s), 3.77 (3H, s).

Example 21(7)

N-benzyloxy-2'-(4-amidinophenylcarbamoyl)-4'-methyl-2-biphenyl carboxamide

[0554]



EP 1 078 917 A1

TLC : Rf 0.52 (Chloroform : Methanol : Water = 10 : 3 : 0.2) ;

NMR (d_6 -DMSO) : δ 11.92 (1H, br.s), 10.83 (1H, s), 9.4-8.8 (3H, br), 7.72 (3H, d, J = 8.8 Hz), 7.52 (2H, d, J = 8.8 Hz), 7.6-7.2 (9H, m), 7.10 (1H, d, J = 7.8 Hz), 7.03 (1H, d, J = 7.8 Hz), 4.75 (2H, s), 2.40 (3H, s).

5 Example 21(8)

N-benzyloxy-2'-(4-amidinophenylcarbamoyl)-4'-methoxy-2-biphenyl carboxamide methanesulfonate

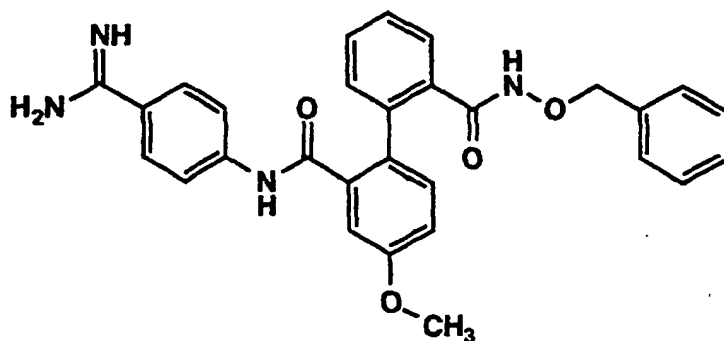
[0555]

10

15

20

25



TLC : Rf 0.62 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (CD_3OD) : δ 7.68 (2H, d, J = 9.0 Hz), 7.58 (2H, d, J = 9.0 Hz), 7.45-7.28 (8H, m), 7.22-7.11 (2H, m), 7.09-7.07 (2H, m), 4.82 (2H, s), 3.88 (3H, s).

30

Example 21(9)

N-benzyloxy-2'-(4-(N^2 -ethoxycarbonylamidino)phenylcarbamoyl)-2-biphenyl carboxamide

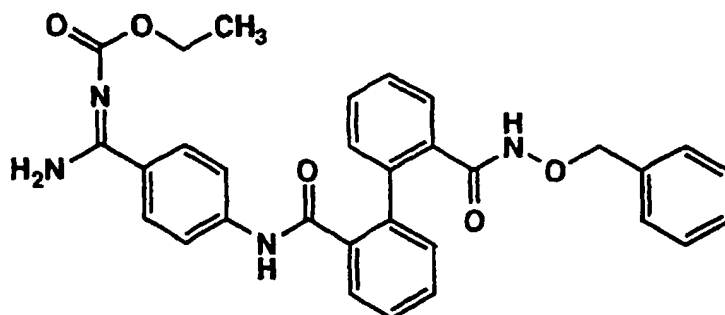
35

[0556]

40

45

50



TLC : Rf 0.58 (Toluene : Ethyl acetate = 1 : 1) ;

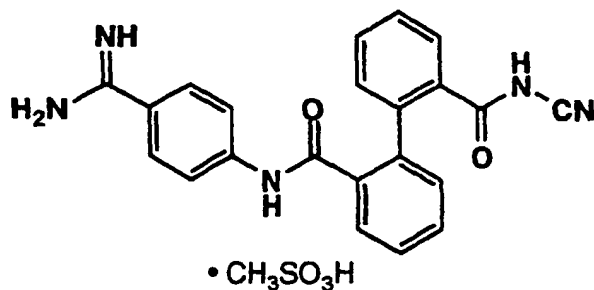
NMR (d_6 -DMSO) : δ 11.85 (1H, br.s), 10.70 (1H, s), 9.2-8.8 (2H, br), 7.85 (2H, d, J = 8.8 Hz), 7.66 (1H, m), 7.6-7.5 (2H, m), 7.5-7.3 (10H, m), 7.2-7.1 (2H, m), 4.71 (2H, s), 4.03 (2H, q, J = 7.4 Hz), 1.20 (3H, t, J = 7.4 Hz).

55

Example 21(10)

N-cyano-2'-(4-amidinophenylcarbamoyl)-2-biphenylcarboxamide methanesulfonate

[0557]

TLC : R_f 0.34 (Ethyl acetate : Acetic acid : Water = 6 : 1 : 0.5) ;NMR (d₆-DMSO) : δ 10.81 (1H, s), 9.17 (2H, br.s), 8.89 (2H, br.s), 7.74 (4H, like s), 7.8-7.4 (6H, m), 7.29 (2H, t, J = 8.0 Hz), 6.0-4.0 (1H, br), 2.35 (3H, s).

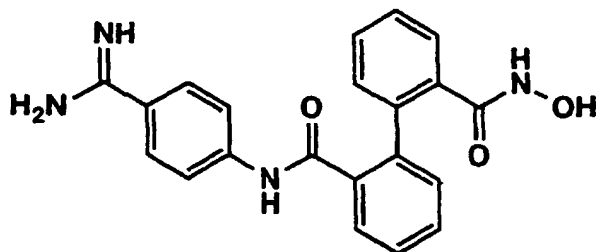
Example 22 — Example 22(9)

[0558] The following compounds were obtained by the same procedure as a series of reaction of Example 2, using the compound prepared in Example 21 — Example 21(9).

Example 22

N-hydroxy-2'-(4-amidinophenylcarbamoyl)-2-biphenylcarboxamide

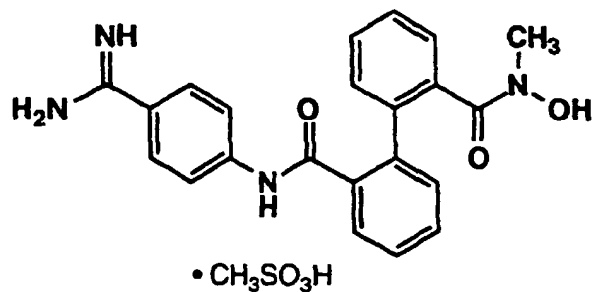
[0559]

TLC : R_f 0.14 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;NMR (d₆-DMSO) : δ 11.8-11.2 (1H, broad), 11.21 (1H, s), 9.7-8.7 (4H, broad), 7.77-7.60 (3H, m), 7.60-7.30 (7H, m), 7.20-7.04 (2H, m).

Example 22(1)

N-hydroxy-N-methyl-2'-(4-amidinophenylcarbamoyl)-2-biphenylcarboxamide methanesulfonate

5 [0560]



20

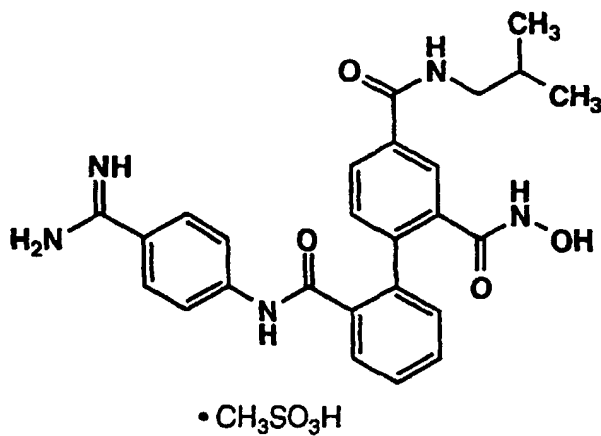
TLC : R_f 0.29 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;NMR (d₆-DMSO) : δ 10.41 (1H, brs), 10.03 (1H, brs), 9.10-8.55 (4H, broad), 7.70 (2H, d, J = 7.0 Hz), 7.67-7.65 (1H, m), 7.53-7.47 (5H, m), 7.37-7.32 (2H, m), 7.31-7.28 (1H, m), 7.15-7.13 (1H, m), 3.21 (3H, s), 2.37 (3H, s).

25

Example 22(2)

N-hydroxy-2'-(4-amidinophenylcarbamoyl)-4-((2-methylpropyl)carbamoyl)-2-biphenylcarboxamide methanesulfonate

30 [0561]



45

50

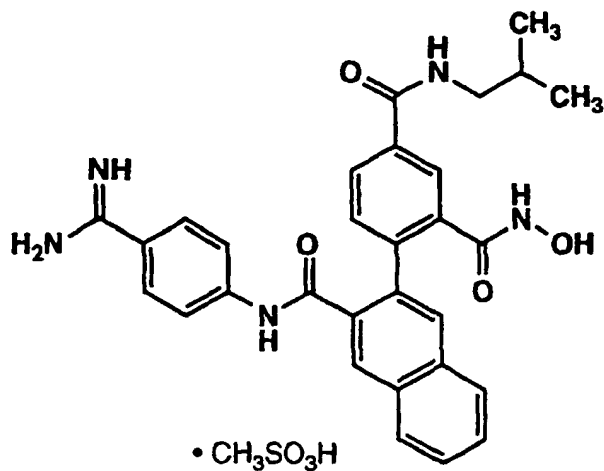
TLC : R_f 0.42 (Chloroform : Methanol : Water = 7 : 3 : 0.3) ;NMR (d₆-DMSO) : δ 11.53 (1H, s), 11.18 (1H, s), 9.13 (2H, s), 8.85 (2H, s), 8.61 (1H, br.t, J = 6.2 Hz), 8.02 (1H, d, J = 1.8 Hz), 7.90 (1H, dd, J = 1.8, 8.0 Hz), 7.68-7.73 (3H, m), 7.54-7.59 (4H, m), 7.23 (1H, d, J = 8.0 Hz), 7.14 (1H, m), 3.06 (2H, t, J = 6.2 Hz), 2.34 (3H, s), 1.82 (1H, m), 0.87 (6H, d, J = 6.6 Hz).

55

Example 22(3)

N-hydroxy-2-(3-(4-amidinophenylcarbamoyl)naphthalen-2-yl)-5-((2-methylpropyl)carbamoyl)benzcarboxamide methanesulfonate

[0562]



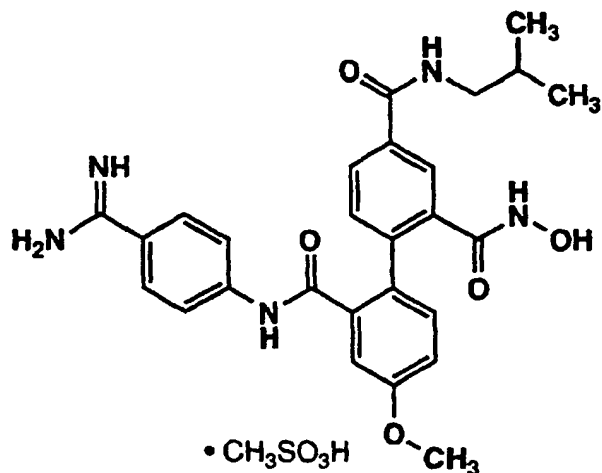
TLC : Rf 0.19 (Chloroform : Methanol : Water = 8 : 2 : 0.2) ;

NMR (d₆-DMSO) : δ 11.49 (1H, s), 11.31 (1H, s), 9.15 (2H, s), 8.81 (2H, s), 8.62 (1H, br.t, J = 5.8 Hz), 8.33 (1H, s), 8.13 (1H, m), 8.06 (1H, d, J = 1.8 Hz), 8.00 (1H, m), 7.93 (1H, dd, J = 1.8, 8.0 Hz), 7.61-7.75 (7H, m), 7.32 (1H, d, J = 8.0 Hz), 3.08 (2H, t, J = 5.8 Hz), 2.34 (3H, s), 1.84 (1H, m), 0.89 (6H, d, J = 6.6 Hz).

Example 22(4)

N-hydroxy-2'-(4-amidinophenylcarbamoyl)-4'-methoxy-4-((2-methylpropyl) carbamoyl)-2-biphenylcarboxamide methanesulfonate

[0563]

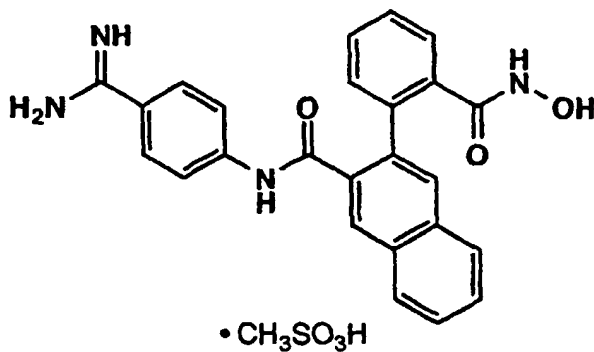


TLC : R_f 0.33 (Chloroform : Methanol : Water = 7 : 3 : 0.3) ;
 NMR (d₆-DMSO) : δ 11.47 (1H, s), 11.18 (1H, s), 9.14 (2H, s), 8.85 (2H, s), 8.60 (1H, br.t, J = 5.8 Hz), 7.99 (1H, d, J = 1.6 Hz), 7.87 (1H, dd, J = 1.6, 8.0 Hz), 7.70 (2H, d, J = 8.8 Hz), 7.57 (2H, d, J = 8.8 Hz), 7.21 (1H, d, J = 2.6 Hz), 7.20 (1H, d, J = 8.0 Hz), 7.14 (1H, dd, J = 2.6, 8.4 Hz), 7.06 (1H, d, J = 8.4 Hz), 3.86 (3H, s), 3.06 (2H, t, J = 5.8 Hz), 2.34 (3H, s), 1.82 (1H, m), 0.87 (6H, d, J = 6.6 Hz).

Example 22(5)

N-hydroxy-2-(3-(4-amidinophenylcarbamoyl)naphthalen-2-yl) benzcarboxamide methanesulfonate

[0564]



EP 1 078 917 A1

TLC : Rf 0.60 (Ethyl acetate : Acetic acid : Water = 3 : 1 : 0.5) ;

NMR (d_6 -DMSO) : δ 11.49 (1H, s), 11.35 (1H, s), 9.5-9.2 (1H, br), 9.15 (2H, br.s), 8.82 (2H, br.s), 8.30 (1H, s), 8.11 (1H, m), 7.98 (1H, m), 7.8-7.2 (10H, m), 7.19 (1H, m), 2.30 (3H, s).

5 Example 22(6)

N-hydroxy-2-(3-(4-amidinophenylcarbamoyl)naphthalen-2-yl)-5-methoxy benzcarboxamide methanesulfonate

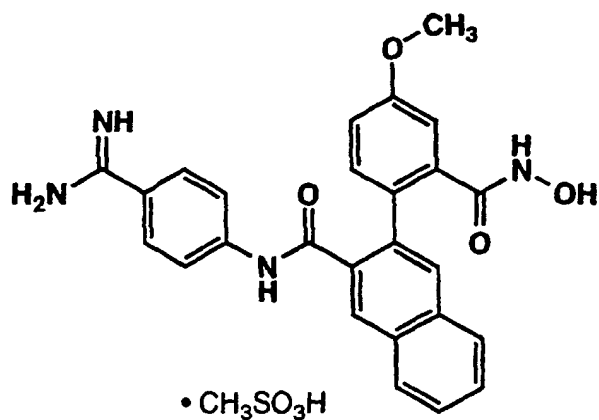
[0565]

10

15

20

25



30

TLC : Rf 0.26 (Chloroform : Methanol : Water = 10 : 3 : 0.2) ;

NMR (d_6 -DMSO) : δ 11.46 (1H, br.s), 11.33 (1H, s), 9.16 (2H, br.s), 8.87 (2H, br.s), 8.27 (1H, s), 8.10 (1H, t, J = 4.4 Hz), 7.96 (1H, t, J = 4.4 Hz), 7.8-7.5 (7H, m), 7.2-6.9 (3H, m), 5.5-4.2 (1H, br), 3.77 (3H, s), 2.35 (3H, s).

35 Example 22(7)

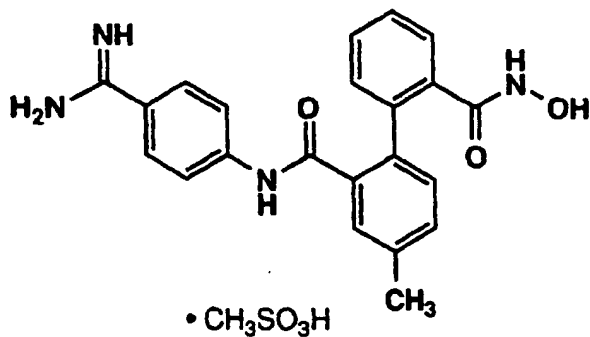
N-hydroxy-2'-(4-amidinophenylcarbamoyl)-4'-methyl-2-biphenylcarboxamide methanesulfonate

[0566]

40

45

50



55

TLC : Rf 0.29 (Chloroform : Methanol : Water = 10 : 3 : 0.2) ;

NMR (d_6 -DMSO) : δ 11.46 (1H, s), 11.17 (1H, s), 9.41 (1H, br), 9.12 (2H, br.s), 8.81 (2H, br.s), 7.68 (2H, d, J = 8.8 Hz), 7.51 (2H, d, J = 8.8 Hz), 7.46 (1H, s), 7.5-7.3 (4H, m), 7.07 (1H, m), 7.01 (1H, d, J = 7.8 Hz), 2.40 (3H, s), 2.31 (3H, s).

5 Example 22(8)

N-hydroxy-2'-(4-amidinophenylcarbamoyl)-4'-methoxy-2-biphenyl carboxamide methanesulfonate

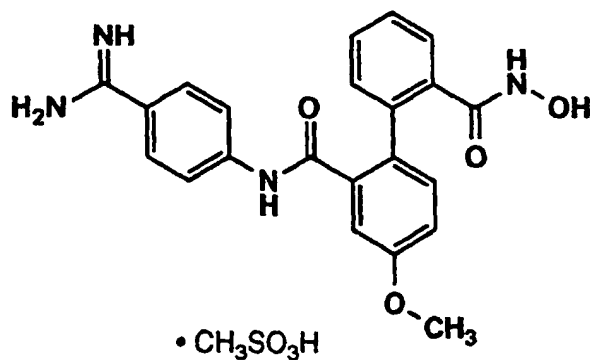
[0567]

10

15

20

25



30

TLC : Rf 0.18 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d_6 -DMSO) : δ 11.46 (1H, s), 11.21 (1H, s), 9.70-9.10 (1H, broad), 9.13 (2H, br.s), 8.89 (2H, br.s), 7.69 (2H, d, J = 9.0 Hz), 7.52 (2H, d, J = 9.0 Hz), 7.50-7.34 (3H, m), 7.20-7.02 (4H, m), 3.84 (3H, s), 2.35 (3H, s).

35 Example 22(9)

35

N-hydroxy-2'-(4-(N²-ethoxycarbonylamidino)phenylcarbamoyl)-2-biphenyl carboxamide

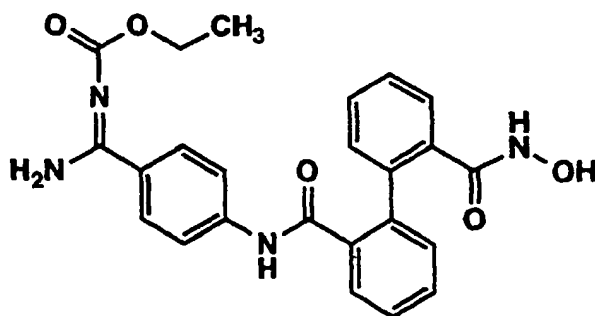
[0568]

40

45

50

55



TLC : Rf 0.59 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d_6 -DMSO) : δ 11.44 (1H, br.s), 10.99 (1H, s), 9.42 (1H, s), 9.3-8.7 (2H, br), 7.83 (2H, d, J = 8.8 Hz), 7.65 (1H,

m), 7.6-7.4 (3H, m), 7.5-7.3 (4H, m), 7.2-7.0 (2H, m), 4.03 (2H, q, $J = 7.4$ Hz), 1.19 (3H, t, $J = 7.4$ Hz).

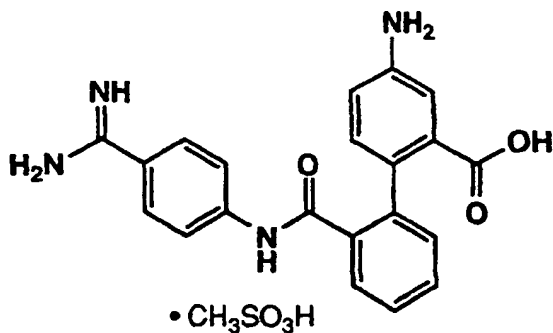
Example 23 — Example 23(1)

- 5 [0569] The following compounds were obtained by the same procedure as a series of reaction of Reference Example 12, using compounds prepared in Example 19(81) and Example 19(72).

Example 23

- 10 2'-(4-amidinophenylcarbamoyl)-4-amino-2-biphenylcarboxylic acid methanesulfonate

[0570]

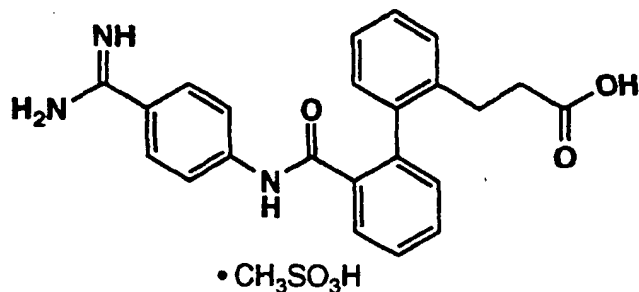


- 30 TLC : R_f 0.11 (Chloroform : Methanol : Water = 7 : 3 : 0.3) ;
NMR (d₆-DMSO) : δ 10.19 (1H, s), 9.13 (2H, brs), 8.88 (2H, brs), 7.73 (2H, d, $J = 9.0$ Hz), 7.63 (2H, d, $J = 9.0$ Hz), 7.57 (1H, dd, $J = 7.0$ Hz, 1.5 Hz), 7.51-7.36 (2H, m), 7.16 (1H, dd, $J = 7.0$ Hz, 1.5 Hz), 6.98 (1H, d, $J = 2.0$ Hz), 6.85 (1H, d, $J = 8.0$ Hz), 6.62 (1H, dd, $J = 8.0$ Hz, 2.0 Hz), 2.35 (3H, s).

- 35 Example 23(1)

3-(2'-(4-amidinophenylcarbamoyl)biphenyl-2-yl)propanoic acid methanesulfonate

[0571]



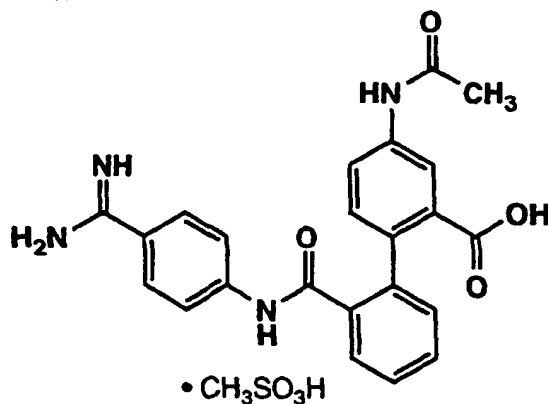
TLC : R_f 0.21 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;
NMR (d₆-DMSO) : δ 12.2-11.9 (1H, broad), 10.55 (1H, s), 9.13 (2H, brs), 8.94 (2H, brs), 7.76-7.50 (7H, m), 7.34-

7.12 (5H, m), 2.76-2.62 (2H, m), 2.45-2.34 (2H, m), 2.36 (3H, s).

Example 24

2'-(4-amidinophenylcarbamoyl)-4-methylcarbonylamino-2-biphenylcarboxylic acid methanesulfonate

[0572]



[0573] To a solution of the compound prepared in Example 23 (376 mg) in dimethylformamide (3.2 ml) and pyridine (0.8 ml), acetic acid anhydrous (75.5 μ l) was added. The mixture was stirred for 1 hour at room temperature. The reaction mixture was concentrated. The residue was crystallized with ethyl acetate, furthermore, was crystallized with ethyl acetate-methanol to give the present compound (407 mg) having the following physical data.

TLC : R_f 0.12 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d₆-DMSO) : δ 13.0-12.5 (1H, broad), 10.43 (1H, s), 10.12 (1H, s), 9.13 (2H, brs), 8.86 (2H, brs), 8.05 (1H, d, J = 2.5 Hz), 7.76-7.60 (6H, m), 7.58-7.42 (2H, m), 7.26-7.20 (1H, m), 7.15 (1H, d, J = 8.0 Hz), 2.34 (3H, s), 2.04 (3H, s).

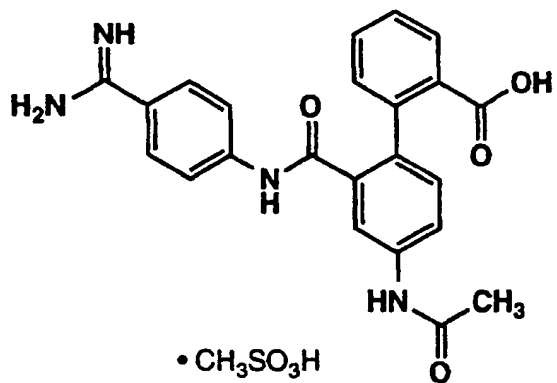
Example 24(1) — Example 24(2)

[0574] The following compounds were obtained by the same procedure as a series of reaction of Example 24, using compounds prepared in Example 19(102) and Example 23.

Example 24(1)

2'-(4-amidinophenylcarbamoyl)-4'-methylcarbonylamino-2-biphenylcarboxylic acid methanesulfonate

5 [0575]

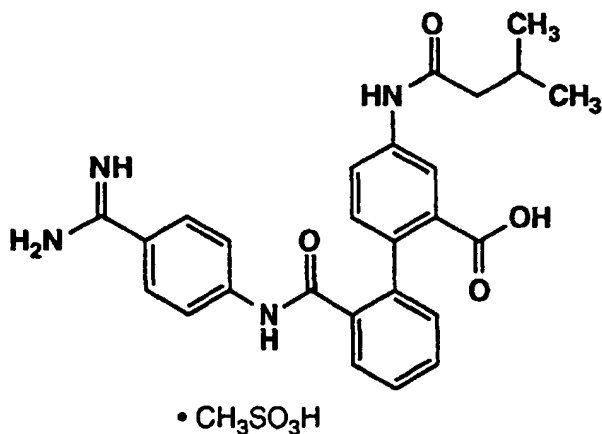


25 TLC : R_f 0.10 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;
 NMR (d₆-DMSO) : δ 10.39 (1H, s), 10.28 (1H, s), 9.19 (2H, brs), 8.96 (2H, brs), 7.89 (1H, d, J = 2.0 Hz), 7.80-7.60 (6H, m), 7.49 (1H, td, J = 7.5 Hz, 1.5 Hz), 7.37 (1H, td, J = 7.5 Hz, 1.5 Hz), 7.22 (1H, dd, J = 7.5 Hz, 1.5 Hz), 7.17 (1H, d, J = 8.0 Hz), 2.35 (3H, s), 2.09 (3H, s).

30 Example 24(2)

2'-(4-amidinophenylcarbamoyl)-4'-((2-methylpropylcarbonyl)amino)-2-biphenylcarboxylic acid methanesulfonate

35 [0576]



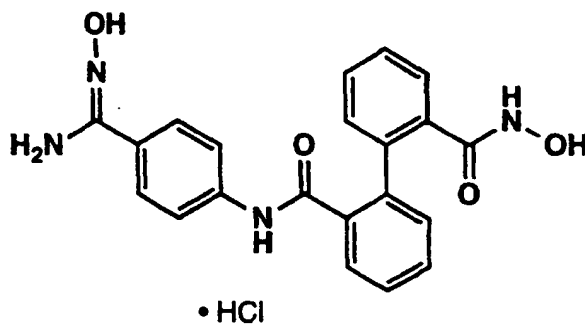
55 TLC : R_f 0.25 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;
 NMR (d₆-DMSO) : δ 13.3-12.2 (1H, broad), 10.43 (1H, s), 10.13 (1H, s), 9.19 (2H, brs), 8.98 (2H, brs), 8.10 (1H, d,

J = 2.5 Hz), 7.78-7.60 (6H, m), 7.56-7.42 (2H, m), 7.26-7.19 (1H, m), 7.15 (1H, d, J = 8.0 Hz), 2.36 (3H, s), 2.19 (2H, d, J = 6.5 Hz), 2.15-1.95 (1H, m), 0.92 (6H, d, J = 6.5 Hz).

Example 25

N-hydroxy-2'-(4-(N²-hydroxyamidino)phenylcarbamoyl)-2-biphenyl carboxamide hydrochloride

[0577]



[0578] 1-Ethyl-3-(3-dimethylaminopropyl)-carbodiimide (183 mg), 1-hydroxybenzotriazole (129 mg) and N-(1-methoxy-1-methylethoxy)amine (333 mg) were added to a solution of the compound prepared in Example 19(158) (302 mg) in dimethylformamide (5 ml). The mixture was stirred for 3 hours at room temperature. The reaction mixture was distilled off an azeotropic mixture with toluene. Methylene chloride (2 ml), methanol (0.5 ml) and 4N hydrochloric acid - dioxane (2 ml) were added to the residue, and the mixture was stirred for 1 hour at room temperature. The reaction mixture was concentrated. The residue was purified by column chromatography on silica gel (Methylene chloride : Methanol : Acetic acid = 10 : 2 : 1). The purified product was dissolved into methanol (2 ml), and then 4N hydrochloric acid - ethyl acetate (0.16 ml) was added to the solution. The mixture was concentrated. The obtained compound hydrochloride was washed with ether to give the present compound (197 mg) having the following physical data.

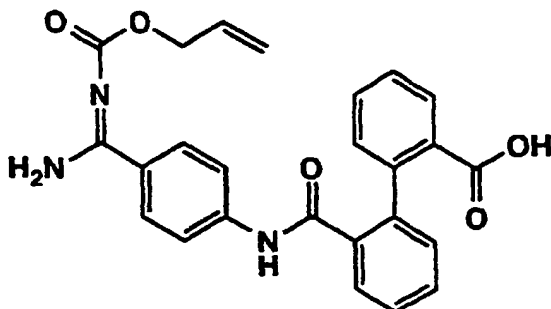
TLC : Rf 0.38 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d₆-DMSO) : δ 12.79 (1H, br), 11.51 (1H, s), 11.19 (1H, s), 11.2-11.0 (1H, br), 9.4-8.7 (3H, br), 7.7-7.4 (8H, m), 7.45-7.35 (2H, m), 7.2-7.0 (2H, m).

Example 26

2'-(4-(N²-(2-propenyl)oxycarbonylamidino)phenylcarbamoyl)-2-biphenyl carboxylic acid

[0579]



[0580] The compound prepared in Example 19 (300 mg) was dissolved into a mixed solution of 2N aqueous solution of sodium hydroxide and tetrahydrofuran (2 : 1, 15 ml), and then allyloxycarbonyl chloride (140 μ l) was added to the solution. The mixture was stirred for 30 minutes at room temperature. 2N hydrochloric acid (10 ml) was added to the reaction mixture. The precipitate obtained by filtration was washed with water, and dried. The precipitate was crystallized with methanol to give the present compound (47 mg) having the following physical data.

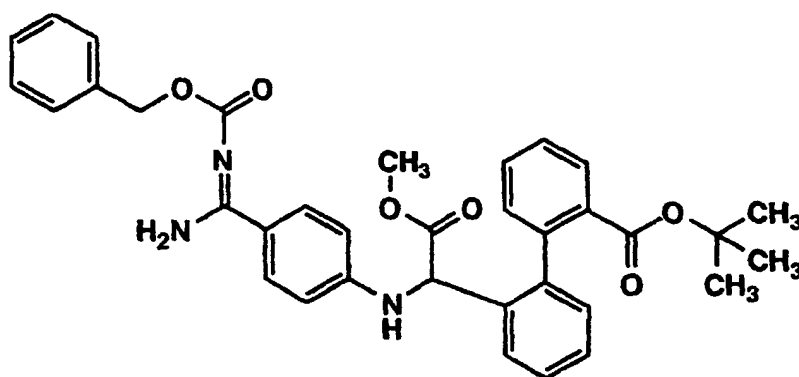
TLC : Rf 0.41 (Chloroform : Methanol : Water = 8 : 2 : 0.2) ;

NMR (d₆-DMSO) : δ 10.32 (1H, s), 9.10 (2H, br.s), 7.89 (2H, d, J = 8.8 Hz), 7.81 (1H, dd, J = 1.8, 7.8 Hz), 7.66 (1H, m), 7.56 (2H, d, J = 8.8 Hz), 7.46-7.54 (3H, m), 7.39 (1H, dt, J = 1.8, 7.8 Hz), 7.21-7.25 (2H, m), 5.96 (1H, m), 5.17-5.35 (2H, m), 4.53-4.56 (2H, m).

Example 27

t-Butyl 2'-(1-(4-(N²-benzyloxycarbonylamidino)phenylamino)-1-methoxy carbonylmethyl)-2-biphenylcarboxylate

[0581]



[0582] t-Butyl 2'-(1-methoxycarbonyl-1-methylsulfonyloxymethyl)-2-biphenyl carboxylate (3.36 g) and 4-(N²-benzyloxycarbonylamidino)aniline (5.38 g) was dissolved into dimethylformamide (5 ml). The mixture was stirred for 19 hours

at 60 °C, and then for 6 hours at 80 °C. After the reaction mixture was cooled to room temperature, water was added to the reaction mixture. The solution was extracted with ethyl acetate. The extract was washed with water, 0.5 N hydrochloric acid, a saturated aqueous solution of sodium bicarbonate and a saturated aqueous solution of sodium chloride, successively, dried over anhydrous sodium sulfate and concentrated. The residue was purified by column chromatography on silica gel (hexane : ethyl acetate = 1 : 1) to give the title compound (2.03 g) having the following physical data.

TLC : R_f 0.53 (Hexane : Ethyl acetate = 1 : 1).

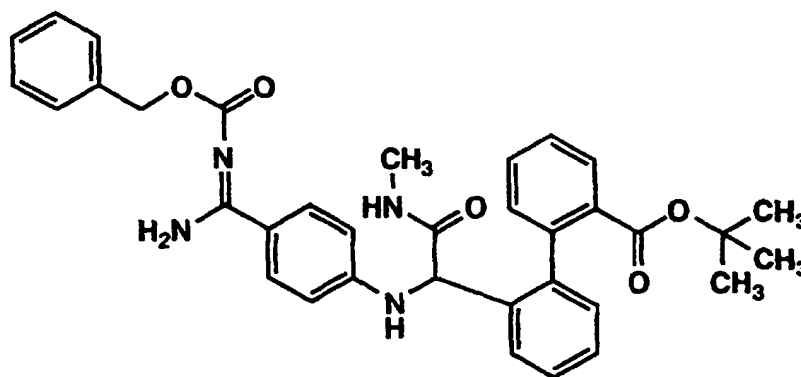
Example 27(1) — Example 27(2)

[0583] The following compounds were obtained by the same procedure as a series of reaction of Example 27, using a corresponding compound instead of t-butyl 2'-(1-methoxycarbonyl-1-methylsulfonyloxymethyl)-2-biphenylcarboxylate.

Example 27(1)

t-Butyl 2'-(1-(4-(N²-benzyloxycarbonylamidino)phenylamino)-1-methyl carbonylmethyl)-2-biphenylcarboxylate

[0584]



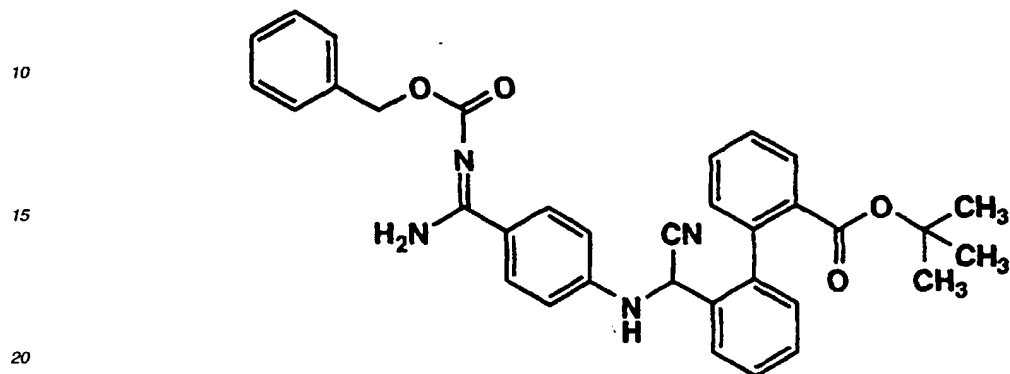
TLC : R_f 0.36 (Chloroform : Ethyl acetate = 1 : 1) ;

NMR (CDCl₃) : δ 10.0-9.0 (2H, broad), 8.0-7.9 (1H, broad), 7.69-7.24 (13H, m), 7.15-7.04 (2H, m), 6.43 and 6.23 (2H, d, J = 9.0 Hz), 5.70 (0.6H, d, J = 2.0 Hz), 5.52 (0.4H, d, J = 5.0 Hz), 5.19 (2H, s), 4.89 (0.4H, d, J = 5.0 Hz), 4.83 (0.6H, d, J = 2.0 Hz), 2.92 and 2.63 (3H, d, J = 5.0 Hz), 1.41 (9H, s).

Example 27(2)

t-Butyl 2'-{1-(4-(N²-benzyloxycarbonylamidino)phenylamino)-1-cyanomethyl)-2-biphenylcarboxylate

5 [0585]



25

TLC : R_f 0.79 (Chloroform : Ethyl acetate = 7 : 3) ;NMR (CDCl₃) : δ 7.97-7.09 (15H, m), 6.47 and 6.36 (2H, d, J = 9.0 Hz), 5.34-5.11 (3H, m), 4.60-4.34 (1H, m), 1.37 and 1.22 (9H, s).

30 Reference Example 17

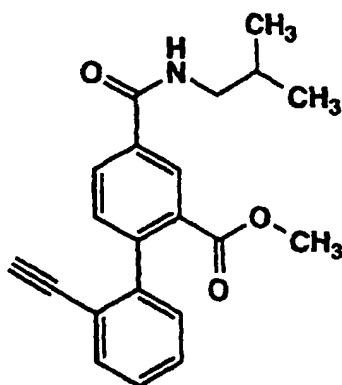
Methyl 2'-ethynyl-4-((2-methylpropyl)carbamoyl)-2-biphenylcarboxylate

35 [0586]

40

45

50



55

[0587] A solution of potassium t-butoxide (1.43 g) in anhydrous tetrahydrofuran (5 ml) was added to a solution of (bromomethyl)triphenylphosphonium bromide (2.78 g) in anhydrous tetrahydrofuran (20 ml). The mixture was stirred for 30 minutes. Methyl 2'-formyl-4-((2-methylpropyl)carbamoyl)-2-biphenylcarboxylate (1.8 g) which was prepared by the same procedure as a series of reaction of Reference Example 3 (using 2-methylpropylamine instead of 2, 2-dimethylpropylamine) → Reference Example 4, using 3-methoxycarbonyl-4-trifluoromethylsulfonyloxybenzoic acid; in anhydrous tetrahydrofuran (20 ml) was added to the mixture. After the mixture was warmed to room temperature, it was

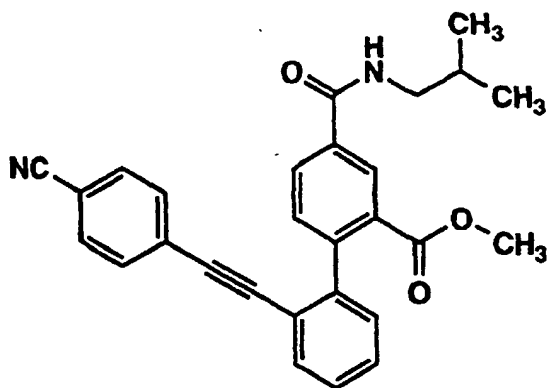
stirred for 12 minutes. Water (100 ml) was added to the reaction mixture, and the solution was extracted with ethyl acetate. The extract was washed with a saturated aqueous solution of sodium chloride, dried over anhydrous magnesium sulfate and concentrated. The residue was purified by column chromatography on silica gel (hexane : ethyl acetate = 2 : 1) to give the title compound (1.20 g) having the following physical data.

TLC : Rf 0.37 (Hexane : Ethyl acetate = 1 : 1) ;

NMR (CDCl₃) : δ 8.32 (1H, d, J = 2.0 Hz), 8.01 (1H, dd, J = 2.0, 8.0 Hz), 7.57 (1H, dd, J = 2.0, 8.0 Hz), 7.43 (1H, d, J = 8.0 Hz), 7.42 (1H, dt, J = 2.0, 8.0 Hz), 7.34 (1H, dt, J = 2.0, 8.0 Hz), 7.24 (1H, dd, J = 2.0, 8.0 Hz), 6.30 (1H, br.t, J = 6.0 Hz), 3.67 (3H, s), 3.33 (2H, t, J = 6.0 Hz), 2.91 (1H, s), 1.94 (1H, m), 1.01 (6H, d, J = 6.6 Hz).

Reference Example 18

Methyl 2'-(4-cyanophenylethynyl)-4-((2-methylpropyl)carbamoyl)-2-biphenylcarboxylate



To a solution of the compound prepared in Reference Example 17 (1.07 g) and p-cyanobromobenzene (640 mg) in dimethylformamide-triethylamine (5 : 1, 6 ml), dichlorobis(triphenylphosphine)palladium (II) (45 mg) was added. The mixture was stirred for 30 minutes 90 °C. Water (100 ml) was added to the reaction mixture, and the solution was extracted with ethyl acetate. The extract was washed with water and a saturated aqueous solution of sodium chloride, successively, dried over anhydrous magnesium sulfate and concentrated. The residue was purified by column chromatography on silica gel (hexane : ethyl acetate = 2 : 1 → 3 : 2) to give the title compound (1.23 g) having the following physical data.

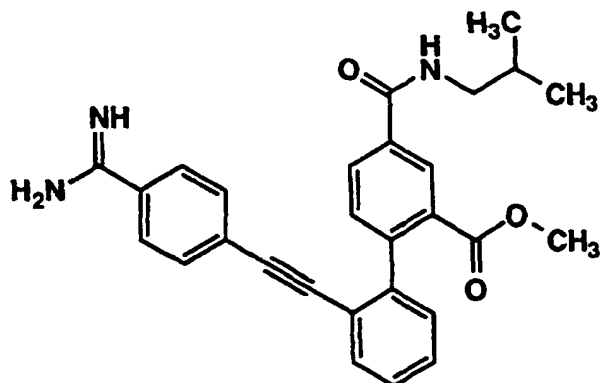
TLC : Rf 0.32 (Hexane : Ethyl acetate = 2 : 1) ;

NMR (CDCl₃) : δ 8.38 (1H, d, J = 2.0 Hz), 8.03 (1H, dd, J = 2.0, 8.0 Hz), 7.61 (1H, d, J = 8.0 Hz), 7.53 (2H, d, J = 8.8 Hz), 7.44-7.50 (2H, m), 7.40 (1H, dt, J = 2.0, 8.0 Hz), 7.27-7.34 (3H, m), 6.36 (1H, br.t, J = 6.4 Hz), 3.63 (3H, s), 3.34 (2H, t, J = 6.4 Hz), 1.95 (1H, m), 1.01 (6H, d, J = 6.6 Hz).

Example 28

Methyl 2'-(4-amidinophenyletynyl)-4-((2-methylpropyl)carbamoyl)-2-biphenylcarboxylate

[0590]



[0591] To a solution of the compound prepared in Reference Example 18 (704 mg) in methanol (20 ml), hydrogen chloride gas was introduced below 10 °C. The solution was stirred for 12 hours at room temperature. The reaction solution was concentrated. To a solution of the residue in methanol (20 ml), ammonium gas was introduced below 10 °C. The solution was stirred for 12 hours at room temperature. The reaction solution was concentrated. The residue was purified by column chromatography on silica gel (Chloroform : Methanol : Water = 9 : 1 : 0.1 → 8 : 2 : 0.2) to give the present compound (0.41 g) having the following physical data.

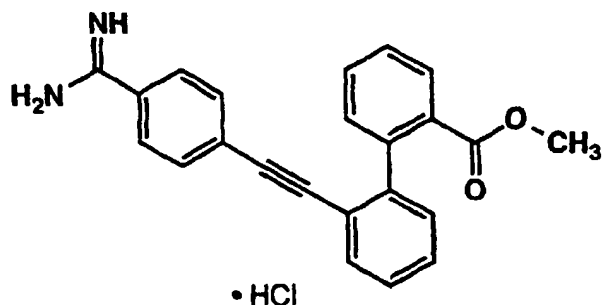
TLC : Rf 0.42 (Chloroform : Methanol : Water = 8 : 2 : 0.2) ;

NMR (CD₃OD) : δ 8.45 (1H, d, J = 2.0 Hz), 8.08 (1H, dd, J = 2.0, 8.0 Hz), 7.71 (2H, d, J = 8.0 Hz), 7.52 (1H, d, J = 8.0 Hz), 7.53 (1H, t, J = 8.0 Hz), 7.50 (1H, t, J = 8.0 Hz), 7.39-7.46 (4H, m), 3.61 (3H, s), 3.25 (2H, d, J = 7.2 Hz), 1.97 (1H, m), 1.00 (6H, d, J = 6.6 Hz).

Example 29

Methyl 2'-(4-amidinophenyletynyl)-2-biphenylcarboxylate hydrochloride

[0592]



[0593] The present compound having the following physical data was obtained by the same procedure as a series of reaction of Reference Example 17 → Reference Example 18 → Example 28, using methyl 2'-formyl-2-biphenylcar-

boxylate.

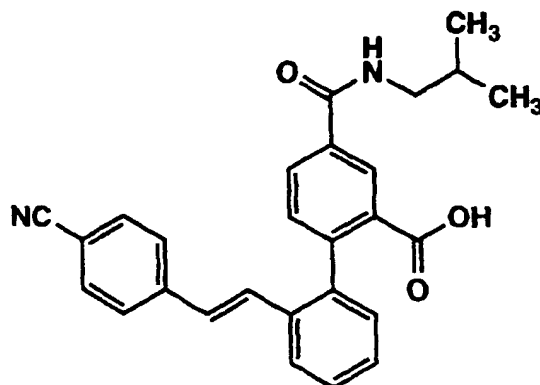
TLC : Rf 0.41 (Chloroform : Methanol : Acetic acid = 20 : 2 : 1) ;

NMR (d_6 -DMSO) : δ 9.30 (4H, brs), 7.94 (1H, dd, J = 2.0, 8.0 Hz), 7.79 (2H, d, J = 8.5 Hz), 7.74-7.38 (7H, m), 7.39 (2H, d, J = 8.5 Hz), 3.52 (3H, s).

Reference Example 19

2'-((1E)-2-(4-cyanophenyl)ethenyl)-4-((2-methylpropyl)carbamoyl)-2-biphenylcarboxylic acid

[0594]



[0595] A solution of p-tolunitrile (1.7 g) and ethyl 2'-formyl-4-((2-methylpropyl)carbamoyl)-2-biphenylcarboxylate (2.58 g) which was prepared by the same procedure as a series of reaction of Reference Example 3 (using 2-methylpropylamine instead of 2, 2-dimethylpropylamine)→ Reference Example 4, using 3-ethoxycarbonyl-4-trifluoromethylsulfonyloxybenzoic acid; in anhydrous hexamethylphosphoramide (3 ml) was added to a solution of potassium t-butoxide in anhydrous hexamethylphosphoramide (30 ml). The mixture was stirred for 12 hours at room temperature. The reaction mixture was diluted with water (100 ml), and extracted with ethyl acetate. The extract was washed with water and a saturated aqueous solution of sodium chloride, successively, dried over anhydrous magnesium sulfate and concentrated. The residue was purified by column chromatography on silica gel (Chloroform : Methanol = 20 : 1 → Chloroform : Methanol : Water = 9 : 1 : 0.1) to give the title compound (0.96 g) having the following physical data.

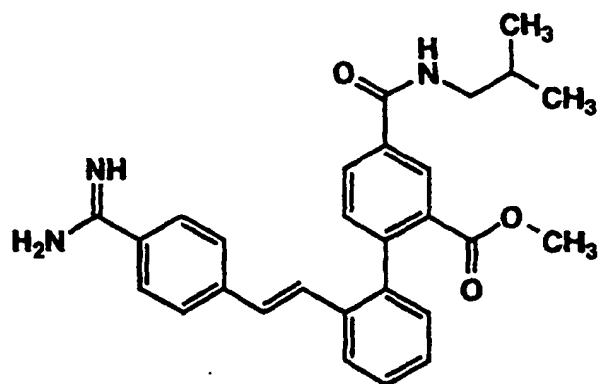
TLC : Rf 0.26 (Chloroform : Methanol : Water = 9 : 1 : 0.1) ;

NMR ($CDCl_3$) : δ 8.40 (1H, s), 8.02 (1H, d, J = 8.0 Hz), 7.71 (1H, d, J = 7.0 Hz), 7.51 (2H, d, J = 8.4 Hz), 7.42 (1H, t, J = 7.0 Hz), 7.36 (1H, t, J = 7.0 Hz), 7.29-7.34 (3H, m), 7.16 (1H, d, J = 7.0 Hz), 6.95 (1H, d, J = 16.0 Hz), 6.85 (1H, d, J = 16.0 Hz), 6.37 (1H, br.t, J = 6.6 Hz), 3.32 (2H, t, J = 6.6 Hz), 1.94 (1H, m), 1.01 (6H, d, J = 6.6 Hz).

Example 30

Methyl 2'-((1E)-2-(4-amidinophenyl)ethenyl)-4-((2-methylpropyl)carbamoyl)-2-biphenylcarboxylate

[0596]



[0597] To a solution of the compound prepared in Reference Example 19 (560 mg) in methanol (20 ml), hydrogen chloride gas was introduced below 10 °C. The solution was stirred for 12 hours at room temperature. The reaction solution was concentrated. To a solution of the residue in methanol (20 ml), ammonium gas was introduced below 10 °C. The solution was stirred for 12 hours at room temperature. The reaction solution was concentrated. The residue was purified by column chromatography on silica gel (Chloroform : Methanol : Water = 9 : 1 : 0.1 → 8 : 2 : 0.2) to give the present compound (0.41 g) having the following physical data.

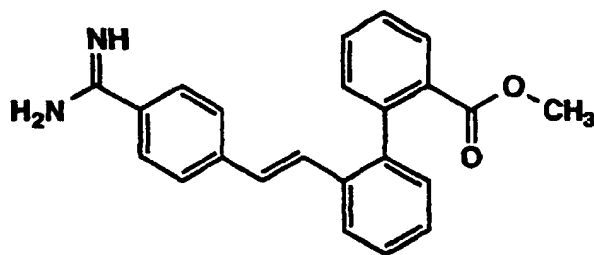
TLC : Rf 0.21 (Chloroform : Methanol : Water = 8 : 2 : 0.2) ;

NMR (d_6 -DMSO): δ 9.23 (2H, s), 8.90 (2H, s), 8.74 (1H, t, J = 6.2 Hz), 8.34 (1H, d, J = 1.8 Hz), 8.13 (1H, dd, J = 1.8, 8.0 Hz), 7.85 (1H, dd, J = 1.8, 8.0 Hz), 7.75 (2H, d, J = 8.8 Hz), 7.54 (2H, d, J = 8.8 Hz), 7.35-7.47 (3H, m), 7.23-7.28 (2H, m), 6.90 (1H, d, J = 16.2 Hz), 3.46 (3H, s), 3.13 (2H, t, J = 6.2 Hz), 2.33 (3H, s), 1.89 (1H, m), 0.92 (6H, d, J = 6.6 Hz).

Example 31

Methyl 2'-((1E)-2-(4-amidinophenyl)ethenyl)-2-biphenylcarboxylate

[0598]



[0599] The present compound having the following physical data was obtained by the same procedure as a series of reaction of Reference Example 19 → Example 30, using ethyl 2'-formyl-2-biphenylcarboxylate.

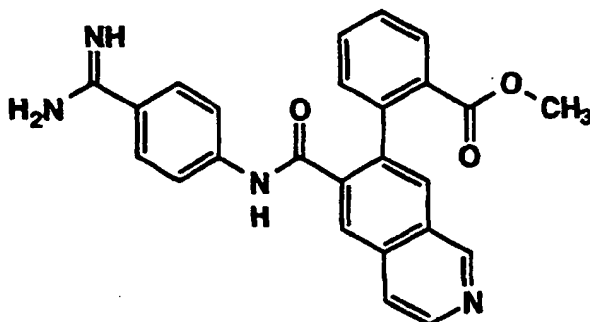
NMR (d_6 -DMSO) : δ 9.60 (2H, brs), 9.20 (2H, brs), 7.88 (1H, dd, J = 1.5, 8.0 Hz), 7.84 (1H, dd, J = 1.5, 8.0 Hz),

7.73 (2H, d, J = 8.5 Hz), 7.60 - 7.40 (2H, m), 7.46 (2H, d, J = 8.5 Hz), 7.36 (2H, brt, J = 8.0 Hz), 7.30 - 7.14 (2H, m), 7.24 (1H, d, J = 16.5 Hz), 6.79 (1H, d, J = 16.5 Hz), 3.58 (3H, s).

Example 32

Methyl 2-(6-(4-amidinophenylcarbamoyl)isoquinolin-7-yl)benzoate

[0600]



[0601] The present compound having the following physical data was obtained by the same procedure as a series of reaction of Reference Example 4 → Reference Example 5 → Reference Example 10 → Reference Example 12 → Example 1, using benzyl 7-trifluoromethylsulfonyloxy-6-isoquinolinecarboxylate.

TLC : Rf 0.36 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (CD₃OD) : δ 9.34 (1H, s), 8.56 (1H, d, J = 6.0 Hz), 8.26 (1H, s), 8.04 (1H, s), 8.00 (1H, d, J = 6.0 Hz), 7.93 (1H, dd, J = 7.5 Hz, 1.5 Hz), 7.73 (4H, s), 7.64 (1H, td, J = 7.5 Hz, 1.5 Hz), 7.52-7.43 (2H, m), 3.61 (3H, s).

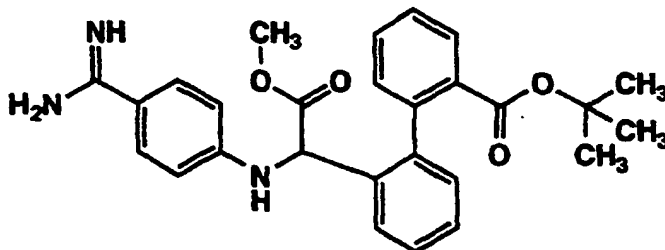
Example 33 — Example 33(7)

[0602] The following compounds were obtained by the same procedure as a series of reaction of Reference Example 19, using a compound prepared in Example 27 — Example 32.

Example 33

t-Butyl 2'-(1-(4-amidinophenylamino)-1-methoxycarbonylmethyl)-2-biphenylcarboxylate

[0603]



EP 1 078 917 A1

TLC : Rf 0.48 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d_6 -DMSO) : δ 7.92-7.83 (1H, m), 7.72-7.10 (9H, m), 6.49-6.39 (2H, m), 4.97 (0.4H, d, J = 9.0 Hz), 4.75 (0.6H, d, J = 75 Hz), 3.57 (3H, s), 1.69 (3H, s), 1.11 (5.4H, s), 1.02 (3.6H, s).

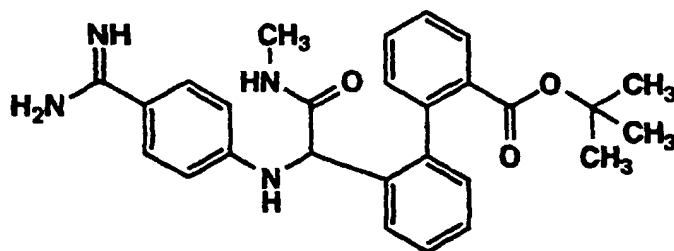
5 Example 33(1)

t-Butyl 2'-(1-(4-amidinophenylamino)-1-methylcarbamoylmethyl)-2-biphenylcarboxylate

[0604]

10

15



20

TLC : Rf 0.65 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

25 NMR (CD_3OD) : δ 7.83 (0.4H, dd, J = 8.0 Hz, 1.5 Hz), 7.65 (0.6H, d, J = 8.0 Hz), 7.56-7.08 (9H, m), 6.50 and 6.37 (2H, d, J = 9.0 Hz), 4.93 and 4.68 (1H, s), 2.80 and 2.71 (3H, s), 1.91 (3H, s), 1.32 and 1.27 (9H, s).

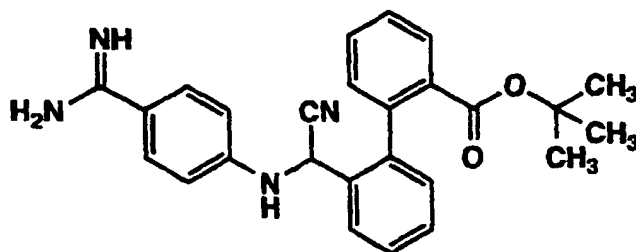
Example 33(2)

30 t-Butyl 2'-(1-(4-amidinophenylamino)-1-cyanomethyl)-2-biphenylcarboxylate

[0605]

35

40



45

TLC : Rf 0.48 and 0.55 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

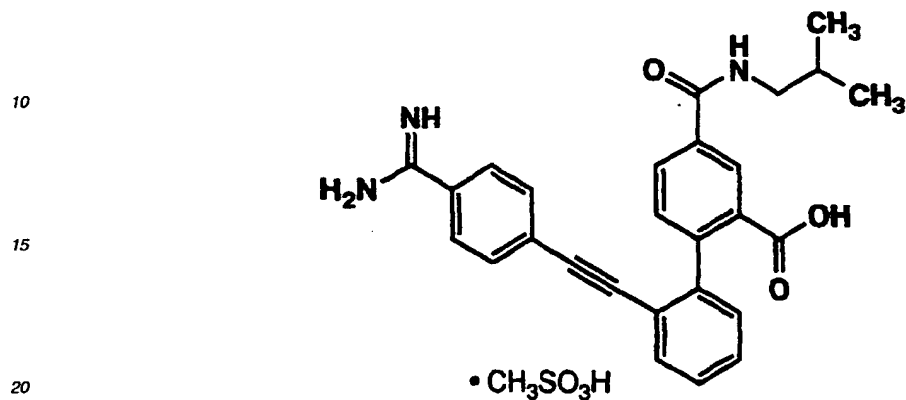
50 NMR (d_6 -DMSO) : δ 7.85-7.10 (10H, m), 6.69 and 6.56 (2H, d, J = 9.0 Hz), 5.52-5.14 (1H, m), 1.10 and 1.13 (9H, s).

55

Example 33(3)

2'-(4-amidinophenylethynyl)-4-((2-methylpropyl)carbamoyl)-2-biphenyl carboxylic acid methanesulfonate

5 [0606]



25

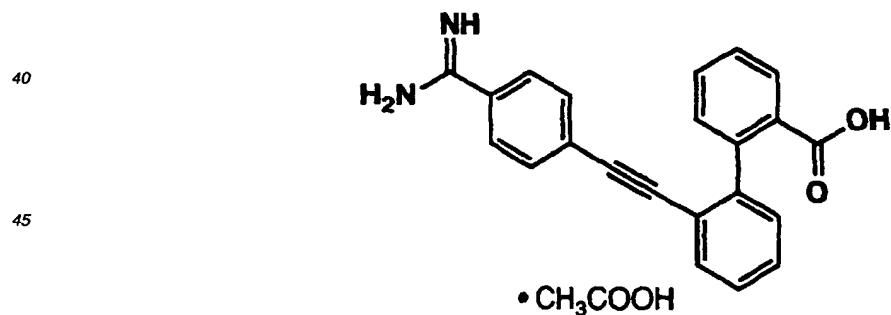
TLC : Rf 0.46 (Chloroform : Methanol : Water = 8 : 2 : 0.2) ;
 NMR (d₆-DMSO) : δ 12.85 (1H, s), 9.33 (2H, s), 9.05 (2H, s), 8.72 (1H, br.t, J = 6.4 Hz), 8.44 (1H, d, J = 1.8 Hz),
 8.11 (1H, dd, J = 1.8, 8.4 Hz), 7.77 (2H, d, J = 8.8 Hz), 7.63 (1H, 1H, d, J = 7.2 Hz), 7.39-7.55 (6H, m), 3.13 (2H, t,
 J = 6.4 Hz), 2.35 (3H, s), 1.89 (1H, m), 0.92 (6H, d, J = 6.8 Hz).

30

Example 33(4)

2'-(4-amidinophenylethynyl)-2-biphenylcarboxylate acetic acetate

35 [0607]



50

55 TLC : Rf 0.37 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;
 NMR (CDCl₃) : δ 11.6-9.00 (4H, m), 7.90 (1H, dd, J = 2.0, 7.5 Hz), 7.73 (2H, d, J = 8.0 Hz), 7.54 (1H, brd, J = 7.5 Hz),
 7.50 - 7.20 (8H, m), 1.84 (3H, s).

Example 33(5)

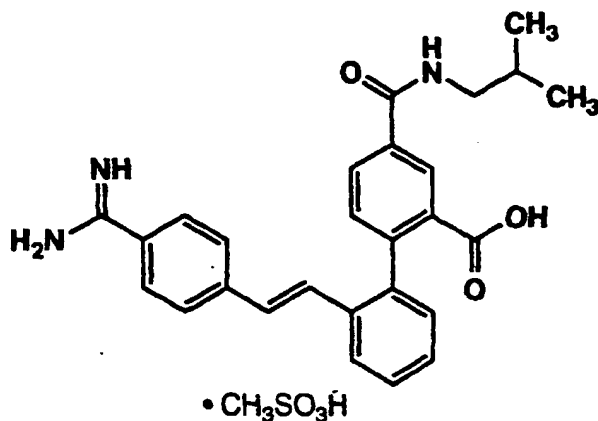
2'-((1E)-2-(4-amidinophenyl)ethenyl)-4-((2-methylpropyl)carbamoyl)-2-biphenylcarboxylic acid methanesulfonate

5 [0608]

10

15

20



25

TLC : R_f 0.39 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d₆-DMSO) : δ 12.78 (1H, s), 9.30 (2H, s), 9.09 (2H, s), 8.75 (1H, br.t, J = 6.0 Hz), 8.39 (1H, s), 8.09 (1H, d, J = 8.0 Hz), 7.87 (1H, d, J = 8.0 Hz), 7.77 (2H, d, J = 8.8 Hz), 7.51 (2H, d, J = 8.8 Hz), 7.44 (1H, t, J = 8.0 Hz), 7.35-7.41 (2H, m), 7.26 (1H, d, J = 16.2 Hz), 7.21 (1H, d, J = 8.0 Hz), 6.93 (1H, d, J = 16.2 Hz), 3.14 (2H, t, J = 6.0 Hz), 2.38 (3H, s), 1.90 (1H, m), 0.92 (6H, d, J = 6.6 Hz).

30

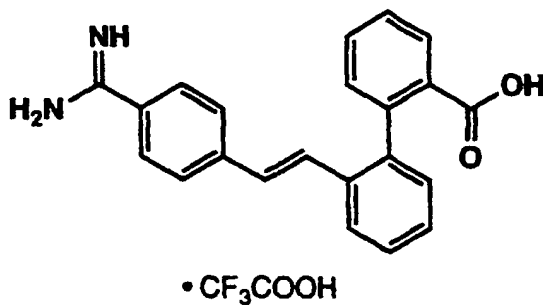
Example 33(6)

2'-((1E)-2-(4-amidinophenyl)ethenyl)-2-biphenylcarboxylic acid trifluoroacetate

[0609]

40

45



50

TLC : R_f 0.25 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d₆-DMSO) : δ 9.60 (2H, brs), 9.20 (2H, brs), 7.88 (1H, dd, J = 1.5, 8.0 Hz), 7.84 (1H, dd, J = 1.5, 8.0 Hz), 7.73 (2H, d, J = 8.5 Hz), 7.60 - 7.40 (2H, m), 7.46 (2H, d, J = 8.5 Hz), 7.36 (2H, brt, J = 8.0 Hz), 7.30 - 7.14 (2H, m), 7.24 (1H, d, J = 16.5 Hz), 6.79 (1H, d, J = 16.5 Hz).

55

Example 33(7)

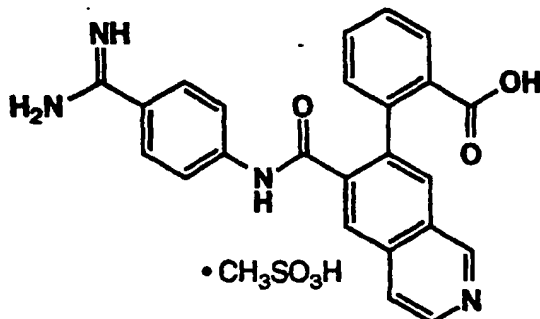
2-(6-(4-amidinophenylcarbamoyl)isoquinolin-7-yl)benzoic acid methanesulfonate

5 [0610]

10

15

20



25 TLC : R_f 0.45 (Ethyl acetate : Acetic acid : Water = 3 : 1 : 1) ;
 NMR (d₆-DMSO) : δ 13.0-12.0 (1H, broad), 10.91 (1H, s), 9.71 (1H, s), 9.20 (2H, brs), 8.94 (2H, brs), 8.72 (1H, d, J = 6.0 Hz), 8.49 (1H, s), 8.38 (1H, d, J = 6.0 Hz), 8.26 (1H, s), 7.93 (1H, dd, J = 7.5 Hz, 1.5 Hz), 7.78 (2H, d, J = 9.0 Hz), 7.73 (2H, d, J = 9.0 Hz), 7.63 (1H, td, J = 7.5 Hz, 1.5 Hz), 7.50 (1H, td, J = 7.5 Hz, 1.5 Hz), 7.39 (1H, dd, J = 7.5 Hz, 1.5 Hz), 2.34 (3H, s).

30 Example 34 — Example 34(2)

[0611] The following compounds were obtained by the same procedure as a series of reaction of Reference Example 19, using a compound prepared in Example 33 — Example 33(2).

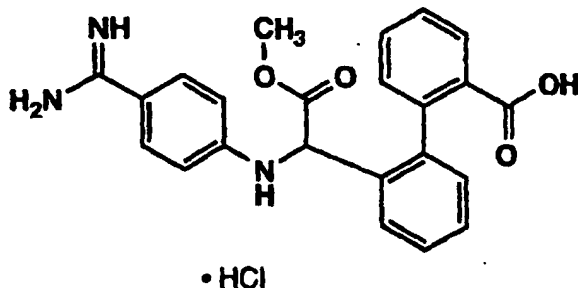
35 Example 34

2'-(1-(4-amidinophenylamino)-1-methoxycarbonylmethyl)-2-biphenyl carboxylic acid hydrochloride

40 [0612]

45

50



55

TLC : R_f 0.39 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;
 NMR (d₆-DMSO) : δ 12.6 (1H, brs), 8.81 (2H, brs), 8.55 (2H, brs), 7.99-7.87 (1H, m), 7.70-7.10 (9H, m), 6.52 and

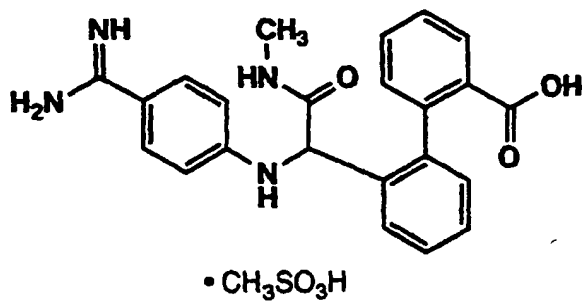
EP 1 078 917 A1

6.47 (2H, d, J = 9.0 Hz), 4.94 and 4.76 (1H, d, J = 7.0 Hz), 3.55 (3H, s).

Example 34(1)

2'-(1-(4-amidinophenylamino)-1-methylcarbamoylmethyl)-2-biphenyl carboxylic acid methanesulfonate

[0613]

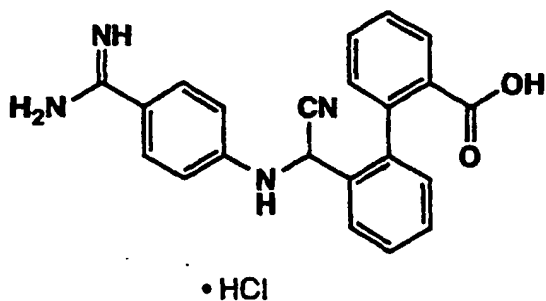


TLC : Rf 0.30 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;
 NMR (CD₃OD) : δ 7.90 (0.4H, dd, J = 8.0 Hz, 2.0 Hz), 7.74 (0.6H, dd, J = 8.0 Hz, 1.0 Hz), 7.54-7.08 (9H, m), 6.48 (0.8H, d, J = 9.0 Hz), 6.39 (1.2H, d, J = 9.0 Hz), 4.84 (0.6H, s), 4.81 (0.4H, s), 2.79 (1.8H, s), 2.71 (3H, s), 2.68 (1.2H, s).

Example 34(2)

2'-(1-(4-amidinophenylamino)-1-cyanomethyl)-2-biphenylcarboxylic acid hydrochloride

[0614]

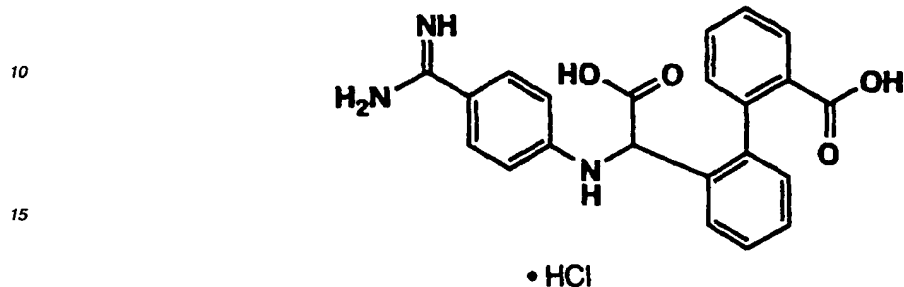


TLC : Rf 0.28 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;
 NMR (CD₃OD) : δ 7.86-7.11 (10H, m), 6.61 (2H, d, J = 8.0 Hz), 5.50 and 5.43 (1H, s).

Example 35

2'-(1-(4-amidinophenylamino)-1-carboxymethyl)-2-biphenylcarboxylic acid hydrochloride

5 [0615]



20

[0616] The present compound having the following physical data was obtained by the same procedure as a series of reaction of Reference Example 19, using a compound prepared in Example 34.

25 TLC : Rf 0.09 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;
 NMR (d_6 -DMSO) : δ 13.8-11.6 (1H, broad), 8.81 and 8.87 (2H, brs), 8.70 (2H, brs), 7.95-7.86 (1H, m), 7.65-7.30 (7H, m), 7.25-7.11 (2H, m), 6.48 and 6.45 (2H, d, $J = 8.5$ Hz), 4.83 and 4.65 (1H, s).

Example 36 — Example 36(1)

30 [0617] The following compounds were obtained by the same procedure as a series of reaction of Example 2, using a compound prepared in Example 33(3) and Example 33(4).

Example 36

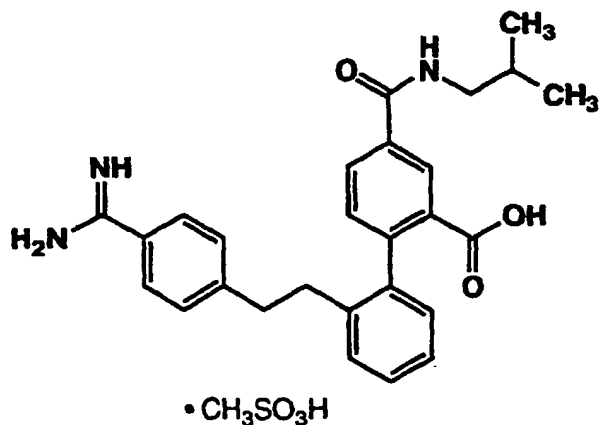
35 2'-(2-(4-amidinophenyl)ethyl)-4-((2-methylpropyl)carbamoyl)-2-biphenyl carboxylic acid methanesulfonate

[0618]

40

45

50



55

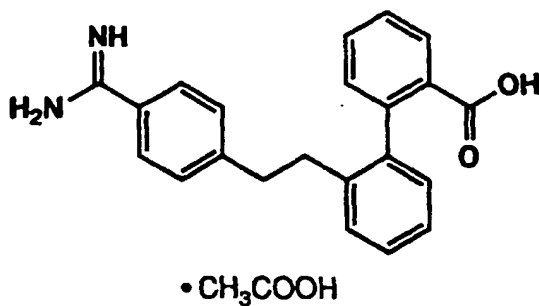
TLC : Rf 0.46 (Chloroform : Methanol : Water = 7 : 3 : 0.3) ;

NMR (d_6 -DMSO) : δ 12.83 (1H, s), 9.19 (2H, s), 9.02 (2H, s), 8.71 (1H, br.t, J = 6.8 Hz), 8.35 (1H, d, J = 2.0 Hz), 8.03 (1H, dd, J = 2.0, 8.0 Hz), 7.64 (2H, d, J = 8.0 Hz), 7.16-7.31 (6H, m), 7.06 (1H, d, J = 8.0 Hz), 3.12 (2H, t, J = 6.8 Hz), 2.61-2.77 (4H, m), 2.33 (3H, s), 1.88 (1H, m), 0.92 (6H, d, J = 7.0 Hz).

Example 36(1)

2'-(2-(4-amidinophenyl)ethyl)-2-biphenylcarboxylic acid acetate

[0619]



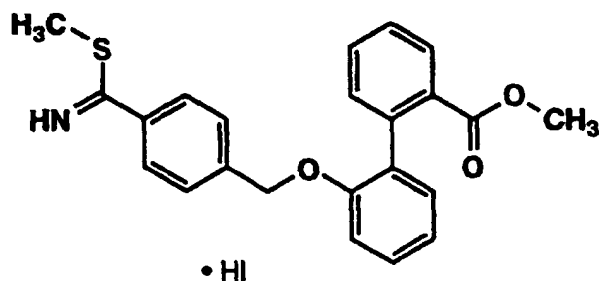
TLC : Rf 0.42 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (CDCl₃) : δ 11.6 - 9.80 (2H, m), 9.80-8.00 (1H, m), 7.79 (1H, dd, J = 2.0, 7.5 Hz), 7.59 (2H, d, J = 8.0 Hz), 7.40 - 7.30 (2H, m), 7.22 - 7.10 (5H, m), 7.10 - 7.00 (2H, m), 1.84 (3H, s).

Reference Example 20

4-(2'-(methoxycarbonylbiphenyl-2-yloxy)methyl)phenylmethylthioimide hydroiodide

[0620]



[0621] To a solution of methyl 2'-(4-cyanobenzoyloxy)-2-biphenylcarboxylate (2.14 g) which was prepared by the same procedure as a series of reaction of Example 16 (using 4-cyanobenzyl bromide instead of a compound prepared in Reference Example 16, and using 2-bromophenol instead of 4-amidinoaniline) → Reference Example 4 → Reference Example 5 → Reference Example 14; in dimethylformamide (40 ml), magnesium chloride hexahydroxide (1.39 mg) and sodium hydrosulfide (629 mg) was added. The mixture was stirred for 4 hours at room temperature. The reaction mixture was diluted with ethyl acetate (100 ml), and the solution was washed with a saturated aqueous solution

of sodium chloride (50 ml, 2 times). The organic layer was dried over anhydrous sodium sulfate and concentrated. The residue was purified by column chromatography on silica gel (hexane : ethyl acetate = 3 : 1) to give thioamide compound (2.74 g). Thioamide compound (2.74 g) was dissolved into acetone (50 ml), and then methyl iodide (1.94 ml) was added to the solution at room temperature. The mixture was refluxed for 1 hour. The reaction mixture was concentrated to give the title compound (3.42 g) having the following physical data.

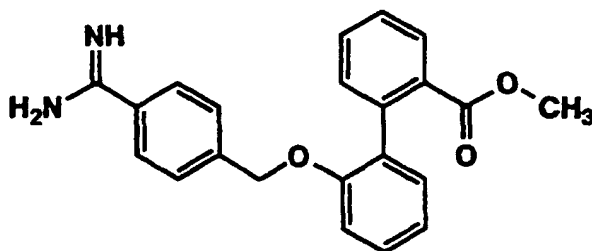
TLC : Rf 0.69 (Chloroform : Methanol = 10 : 1) ;

NMR (CDCl₃) : δ 8.01 (2H, d, J = 8.5 Hz), 7.94 (1H, dd, J = 1.5, 7.5 Hz), 7.58 (1H, dt, J = 1.5, 7.5 Hz), 7.44 (1H, dt, J = 1.5, 7.5 Hz), 7.38 (2H, d, J = 8.5 Hz), 7.4-7.25 (5H, m), 7.09 (1H, dt, J = 1.5, 7.5 Hz), 6.90 (1H, br.d, J = 7.5 Hz), 5.07 (2H, s), 3.60 (3H, s), 3.13 (3H, s).

Example 37

Methyl 2'-(4-amidinobenzyloxy)-2-biphenylcarboxylate

[0622]



[0623] The compound prepared in Reference Example 20 (3.23 g) and ammonium acetate (959 mg) was dissolved into ethanol (50 ml). The mixture was refluxed for 1 hour. The reaction mixture was cooled to room temperature, and concentrated. The residue was purified by column chromatography on silica gel (Chloroform : Methanol = 10 : 1 → Chloroform : Methanol : Water = 10 : 2 : 0.1) to give the present compound (2.15 g) having the following physical data.

TLC : Rf 0.38 (Chloroform : Methanol : Acetic acid = 10 : 1 : 0.2) ;

NMR (d₆-DMSO) : δ 9.4-8.83 (4H, br), 7.80 (1H, dd, J = 1.0, 8.0 Hz), 7.73 (2H, d, J = 8.4 Hz), 7.63 (1H, dt, J = 1.0, 8.0 Hz), 7.48 (1H, dt, J = 1.0, 8.0 Hz), 7.42 (2H, d, J = 8.4 Hz), 7.4-7.25 (2H, m), 7.21 (1H, dd, J = 1.0, 8.0 Hz), 7.1-7.0 (2H, m), 5.15 (2H, s), 3.52 (3H, s).

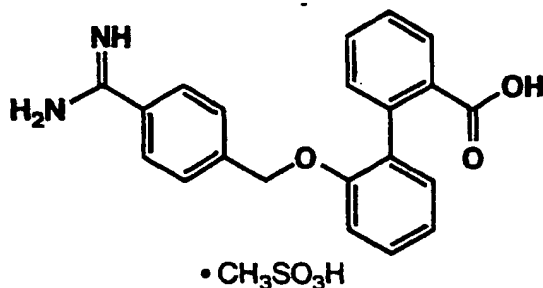
Example 38

2'-(4-amidinobenzyloxy)-2-biphenylcarboxylic acid methanesulfonate

5 [0624]

10

15



20

[0625] The present compound having the following physical data was obtained by the same procedure as a series of reaction of Example 19, using the compound prepared in Example 37.

25

TLC : R_f 0.60 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d₆-DMSO) : δ 12.46 (1H, br.s), 9.24 (2H, s), 8.91 (2H, s), 7.82 (1H, dd, J = 1.0, 7.5 Hz), 7.72 (2H, d, J = 8.4 Hz), 7.58 (1H, dt, J = 1.0, 7.5 Hz), 7.5-7.4 (1H, m), 7.46 (2H, d, J = 8.4 Hz), 7.35-7.25 (2H, m), 7.18 (1H, dd, J = 1.0, 7.5 Hz), 7.05-6.95 (2H, m), 5.15 (2H, s), 2.31 (3H, s).

Reference Example 21

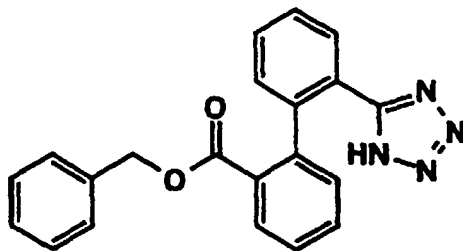
30

Benzyl 2'-(tetrazol-5-yl)-2-biphenylcarboxylate

[0626]

35

40



45

[0627] To a solution of benzyl 2'-cyano-2-biphenylcarboxylate (560 mg) in toluene (10 ml), azidotrimethyltin (810 mg) was added. The mixture was refluxed for 12 hours. The reaction mixture was concentrated. 5% aqueous solution of potassium fluoride (4 ml) was added to the residue. The solution was filtered. The filtrate was diluted with ethyl acetate, and the solution was washed with a saturated aqueous solution of sodium chloride. The organic layer was dried over anhydrous sodium sulfate and concentrated. The residue was purified by column chromatography on silica gel (hexane : ethyl acetate = 2 : 1 → chloroform : methanol = 10 : 1) to give the title compound (545 mg) having the following physical data.

55

TLC : R_f 0.08 (Hexane : Ethyl acetate = 2 : 1).

Reference Example 22

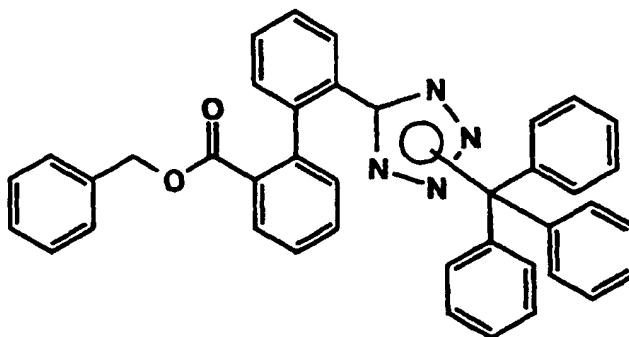
Benzyl 2'-(triphenylmethyltetrazol-5-yl)-2-biphenylcarboxylate

5 [0628]

10

15

20



25

[0629] Triethylamine (2.74 ml) and trityl chloride (549 mg) were added to a solution of the compound prepared in Reference Example 21 (545 mg) in methylene chloride (10 ml). The mixture was stirred for 1 hour at room temperature. The reaction mixture was diluted with chloroform (50 ml), and the solution was washed with water (50 ml). The organic layer was dried over anhydrous sodium sulfate and concentrated. The residue was purified by column chromatography on silica gel (hexane : ethyl acetate = 8 : 1) to give the title compound (713 mg) having the following physical data.

30

TLC : Rf 0.71 (Hexane : Ethyl acetate = 2 : 1).

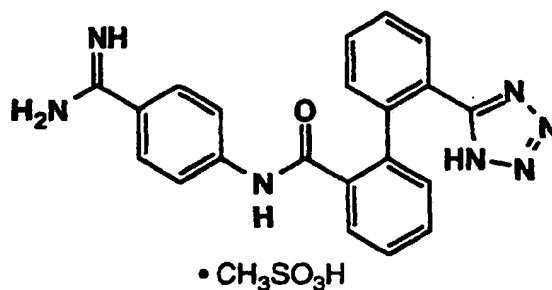
Example 39

2'-(4-amidinophenylcarbamoyl)-2-(tetrazol-5-yl)biphenyl methanesulfonate

35 [0630]

40

45



50

[0631] The present compound having the following physical data was obtained by the same procedure as a series of reaction of Example 11 → Example 1 → Example 2, using a compound prepared in Reference Example 22.

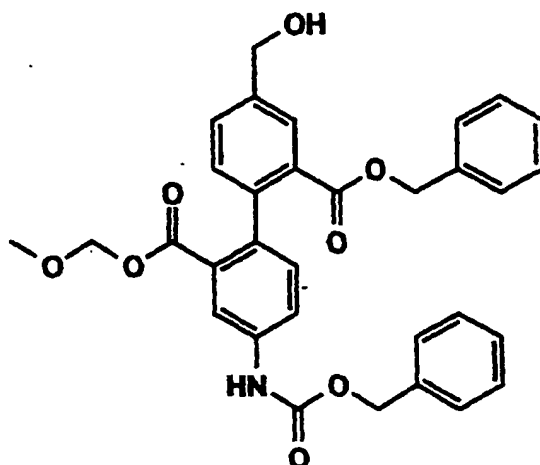
55

TLC : Rf 0.35 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;
 NMR (d_6 -DMSO) : δ 10.32 (1H, s), 9.14 (2H, s), 8.80 (2H, s), 7.71 (2H, d, J = 9.0 Hz), 7.7-7.45 (6H, m), 7.63 (2H, d, J = 9.0 Hz), 7.42 (1H, dd, J = 1.2, 7.5 Hz), 7.24 (1H, dd, J = 1.2, 7.5 Hz), 4.2-3.5 (1H, br), 2.32 (3H, s).

Reference Example 23

Benzyl 4'-benzyloxycarbonylamino-2'-methoxymethyloxycarbonyl-4-hydroxymethyl-2-biphenylcarboxylate

[0632]



[0633] To a solution of benzyl 4'-benzyloxycarbonylamino-2'-methoxymethyloxycarbonyl-4-t-butyldiphenylsilyloxymethyl-2-biphenyl carboxylate (777 mg) which was prepared by the same procedure as a series of reaction of Reference Example 6 → Reference Example 1 (without an esterification of benzyl) → Reference Example 4 → Reference Example 5 → Reference Example 7, using 5-benzyloxycarbonylaminosalicylic acid; in anhydrous tetrahydrofuran (10 ml), a solution of 1.0M tetrabutylammonium fluoride in anhydrous tetrahydrofuran (1.0 ml) was added. The mixture was stirred for 2 hours at room temperature. Water (100 ml) was added to the reaction mixture, the solution was extracted with ethyl acetate. The organic layer was washed with a saturated aqueous solution of sodium chloride, successively, dried over anhydrous magnesium sulfate and concentrated. The residue was purified by column chromatography on silica gel (n-hexane : ethyl acetate = 2 : 3) to give the title compound (370 mg) having the following physical data.

TLC : Rf 0.29 (n-Hexane : Ethyl acetate = 1 : 1) ;

NMR(200 MHz, CDCl₃) : δ 8.02 (d, J = 2.0 Hz, 1H), 7.81 (d, J = 2.0 Hz, 1H), 7.65 (dd, J = 8.0, 2.0 Hz, 1H), 7.54 (dd, J = 8.0, 2.0 Hz, 1H), 7.45-7.38 (m, 5H), 7.28-7.07 (m, 7H), 6.78 (s, 1H), 5.25 (s, 2H), 5.16 (d, J = 6.0 Hz, 1H), 5.10 (d, J = 6.0 Hz, 1H), 5.04 (s, 2H), 4.76 (s, 2H), 3.21 (s, 3H).

Reference Example 24

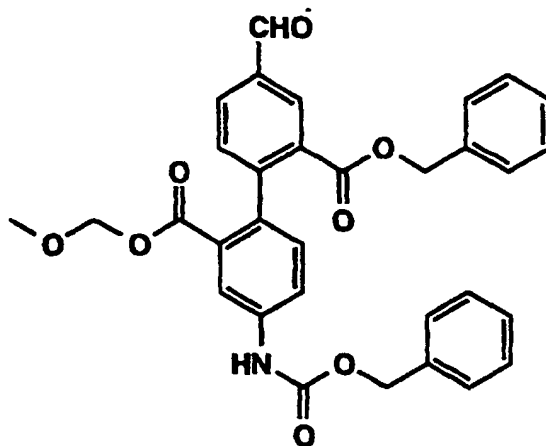
Benzyl 4'-benzyloxycarbonylamino-2'-methoxymethyloxycarbonyl-4-formyl-2-biphenylcarboxylate

5 [0634]

10

15

20



25

[0635] Dimethylsulfoxide (124 μ l) was added to a solution of oxalyl chloride (120 μ l) in anhydrous methylene chloride (5 ml) at -78 °C. The mixture was stirred for 10 minutes. The compound prepared in Reference Example 23 (370 mg) in anhydrous methylene chloride (5 ml) was added to the above solution at -78°C. The mixture was stirred for 1 hour. Triethylamine (0.38 ml) was added to the reaction mixture at -78 °C. The mixture was stirred for 1 hour at room temperature. Water (50 ml) was added to the reaction mixture at -78 °C. The solution was extracted with ethyl acetate. The organic layer was washed with a saturated aqueous solution of sodium chloride, successively, dried over anhydrous magnesium sulfate and concentrated to give the title compound (356 mg) having the following physical data.

30

35

TLC : Rf 0.65 (n-Hexane : Ethyl acetate = 1 : 1) ;

NMR(200 MHz, CDCl_3) : δ 10.09 (s, 1H), 8.53 (d, J = 2.0 Hz, 1H), 8.04 (dd, J = 8.0, 2.0 Hz, 1H), 7.86 (d, J = 2.0 Hz, 1H), 7.71 (dd, J = 8.0, 2.0 Hz, 1H), 7.46-7.35 (m, 5H), 7.26-7.24 (m, 4H), 7.17-7.08 (m, 3H), 6.75 (s, 1H), 5.26 (s, 2H), 5.16 (d, J = 6.4 Hz, 1H), 5.12 (d, J = 6.4 Hz, 1H), 5.08 (s, 2H), 3.25 (s, 3H).

40

45

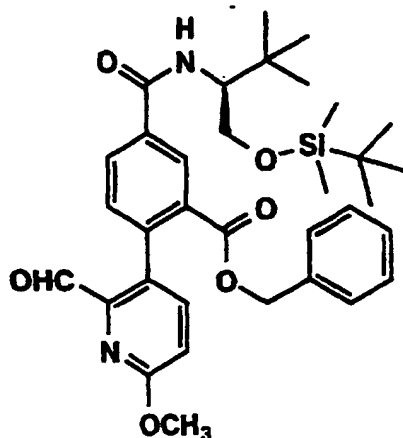
50

55

Reference Example 25

Benzyl 2-(2-formyl-6-methoxy-3-pyridyl)-5-((1(S)-t-butyl dimethylsilyloxymethyl-2, 2-dimethylpropyl)carbamoyl)benzoate

[0636]



[0637] To a solution of 3-tributyltin-2-formyl-6-methoxypyridine (2.45 g) and benzyl 2-trifluoromethylsulfonyloxy-5-((1(R)-t-butylmethylsilyloxymethyl-2, 2-dimethylpropyl)carbamoyl)benzoate (2.36 g) which was prepared by the same procedure as a series of reaction of Reference Example 1 → Reference Example 2 → Reference Example 3, using a corresponding compound; in dimethylformamide (15 ml), copper oxide (II) (305 mg) and dichlorobis(triphenylphosphine)palladium (II) (134 mg) were added. The mixture was stirred for 1 hour at 110 °C. The reaction mixture was cooled to room temperature, and ethyl acetate and water were added to the reaction solution. Insoluble solid was removed by filtration. The filtrate was extracted. The organic layer was washed two times with water, and a saturated aqueous solution of sodium chloride, dried over anhydrous magnesium sulfate and concentrated. The residue was purified by column chromatography on silica gel (hexane : ethyl acetate = 7 : 3) to give the present compound (2.02 g) having the following physical data.

TLC : R_f 0.51 (Hexane : Ethyl acetate = 7 : 3) ;

NMR (300 MHz, CDCl₃) : δ 9.78 (s, 1H), 8.49 and 8.46 (d, J = 2.0 Hz, 1H), 8.00 and 7.97 (dd, J = 8.0, 2.0 Hz, 1H), 7.39 (d, J = 8.0 Hz, 1H), 7.32-7.27 (m, 4H), 7.19-7.12 (m, 2H), 6.87 (d, J = 8.0 Hz, 1H), 6.63 (d, J = 9.6 Hz, 1H), 5.08 (s, 2H), 4.06-4.00 (m, 1H), 4.03 (s, 3H), 3.91 (dd, J = 10.5, 3.3 Hz, 1H), 3.76 (dd, J = 10.5, 4.5 Hz, 1H), 1.04 (s, 9H), 0.88 (s, 9H), 0.07 (s, 3H), 0.04 (s, 3H).

Example 40(1) — 40(88)

[0638] The following compounds were obtained by the same procedure as a series of reaction of Example 1, using a compound prepared by the same procedure as a series of reaction of Reference Example 1 → Reference Example 2 → Reference Example 3 → Reference Example 4 or Reference Example 25 → Reference Example 5 using a corresponding compound instead of a compound prepared in Reference Example 5, or using a compound prepared by the same procedure as a series of reaction of Reference Example 5 → Reference Example 3 → Example 4 using the compound prepared in Reference Example 24 or a compound prepared by the same procedure as it, and using a corresponding compound instead of 4-amidinoaniline.

Example 40(1)

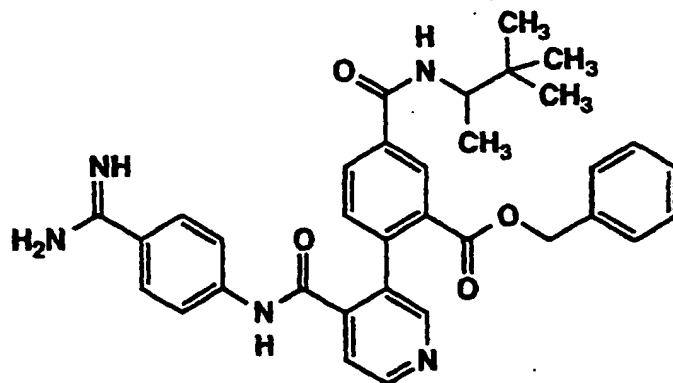
Benzyl 2-[4-(4-amidinophenylcarbamoyl)-3-pyridyl]-5-[(1, 2, 2-trimethyl propyl)carbamoyl]benzoate

5 [0639]

10

15

20



25

TLC : Rf 0.27 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;
 NMR (200 MHz, CD₃OD) : δ 8.64 (1H, d, J = 5.0 Hz), 8.50 (1H, s), 8.39 (1H, d, J = 2.0 Hz), 8.00 (1H, dd, J = 8.0 Hz, 2.0 Hz), 7.70 (4H, s), 7.61 (1H, d, J = 5.0 Hz), 7.47 (1H, d, J = 8.0 Hz), 7.30-7.23 (3H, m), 7.23-7.13 (2H, m), 5.11 (2H, s), 4.05 (1H, q, J = 7.0 Hz), 1.16 (3H, d, J = 7.0 Hz), 0.96 (9H, s).

30

Example 40(2)

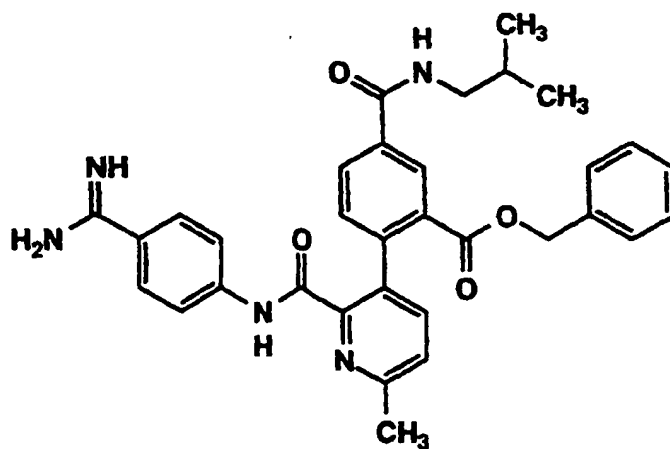
Benzyl 2-[2-(4-amidinophenylcarbamoyl)-6-methyl-3-pyridyl]-5-[(2-methyl propyl)carbamoyl]benzoate

35 [0640]

40

45

50



55

TLC : Rf 0.49 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;
 NMR (300 MHz, CD₃OD) : δ 8.52 (1H, d, J = 2.0 Hz), 8.03 (1H, dd, J = 8.0 Hz, 2.0 Hz), 7.85 (2H, d, J = 9.0 Hz),

EP 1 078 917 A1

7.76 (2H, d, J = 9.0 Hz), 7.55 (1H, d, J = 7.5 Hz), 7.43 (1H, d, J = 7.5 Hz), 7.32 (1H, d, J = 8.0 Hz), 7.27-7.16 (3H, m), 7.09-7.03 (2H, m), 5.04 (1H, brd, J = 12 Hz), 4.98 (1H, brd, J = 12 Hz), 3.23 (2H, d, J = 7.0 Hz), 2.64 (3H, s), 2.03-1.88 (1H, m), 0.98 (6H, d, J = 6.5 Hz).

5 Example 40(3)

Benzyl 2-[2-(4-amidinophenylcarbamoyl)-6-methyl-3-pyridyl]-5-[(1, 2, 2-trimethylpropyl)carbamoyl]benzoate

[0641]

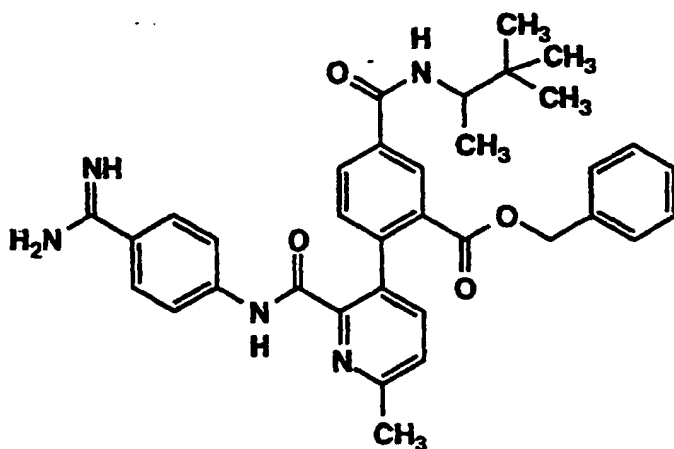
10

15

20

25

30



35

TLC : Rf 0.51 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (300 MHz, CD₃OD) : δ 8.48 (1H, d, J = 2.0 Hz), 8.00 (1H, dd, J = 8.0 Hz, 2.0 Hz), 7.85 (2H, d, J = 9.0 Hz), 7.76 (2H, d, J = 9.0 Hz), 7.56 (1H, d, J = 8.0 Hz), 7.43 (1H, d, J = 8.0 Hz), 7.32 (1H, d, J = 8.0 Hz), 7.28-7.16 (3H, m), 7.10-7.06 (2H, m), 5.05 (1H, brd, J = 12 Hz), 4.98 (1H, brd, J = 12 Hz), 4.10 (1H, q, J = 7.0 Hz), 2.64 (3H, s), 1.20 (3H, d, J = 7.0 Hz), 1.00 (9H, s).

40

45

50

55

Example 40(4)

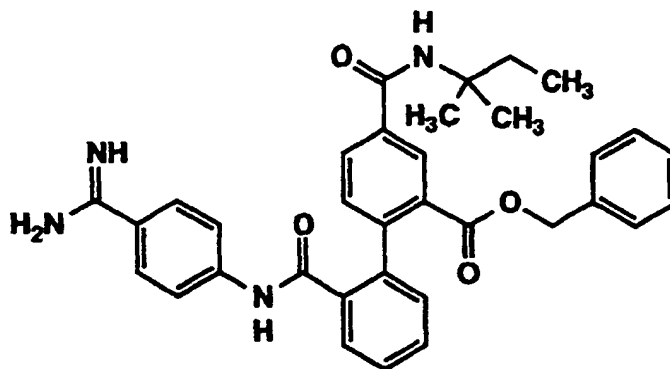
Benzyl 2'-(4-amidinophenylcarbamoyl)-4-(1, 1-dimethylpropylcarbamoyl)-2-biphenylcarboxylate

5 [0642]

10

15

20



25

TLC : Rf 0.39 (Chloroform : Methanol : Water = 8 : 2 : 0.1) ;
 NMR (300 MHz, CD₃OD) : δ 8.21 (d, J = 1.8 Hz, 1H), 7.88 (dd, J = 7.8, 1.8 Hz, 1H), 7.67 (d, J = 9.0 Hz, 2H), 7.68-7.64 (m, 1H), 7.60 (d, J = 9.0 Hz, 2H), 7.56-7.46 (m, 2H), 7.39 (d, J = 7.8 Hz, 1H), 7.28-7.24 (m, 4H), 7.16-7.13 (m, 2H), 5.12 (s, 2H), 1.85 (q, J = 7.5 Hz, 2H), 1.38 (s, 6H), 0.88 (t, J = 7.5 Hz, 3H).

30 Example 40(5)

Benzyl 2'-(4-amidinophenylcarbamoyl)-4-[(1(S)-t-butyl-2-methoxycarbonyl ethyl)carbamoyl]-2-biphenylcarboxylate

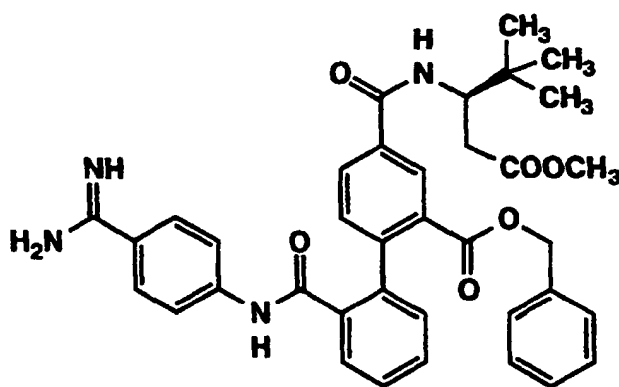
35 [0643]

35

40

45

50



55

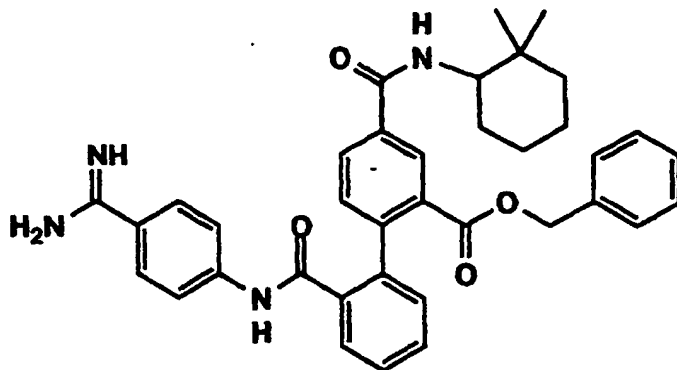
TLC : Rf 0.37 (Chloroform : Methanol : Water = 8 : 2 : 0.1) ;
 NMR (200 MHz, CD₃OD) : δ 8.25 (d, J = 1.8 Hz, 1H), 7.92 (dd, J = 8.0, 1.8 Hz, 1H), 7.70-7.49 (m, 7H), 7.42 (d, J = 7.8 Hz, 1H), 7.29-7.25 (m, 4H), 7.18-7.15 (m, 2H), 5.12 (s, 2H), 4.39 (dd, J = 11.4, 3.2 Hz, 1H), 3.56 (s, 3H), 2.72

(dd, J = 14.6, 3.2 Hz, 1H), 2.53 (dd, J = 14.6, 11.4 Hz, 1H), 0.97 (s, 9H).

Example 40(6)

5 Benzyl 2'-(4-amidinophenylcarbamoyl)-4-(2, 2-dimethylcyclohexylcarbamoyl)-2-biphenylcarboxylate

[0644]



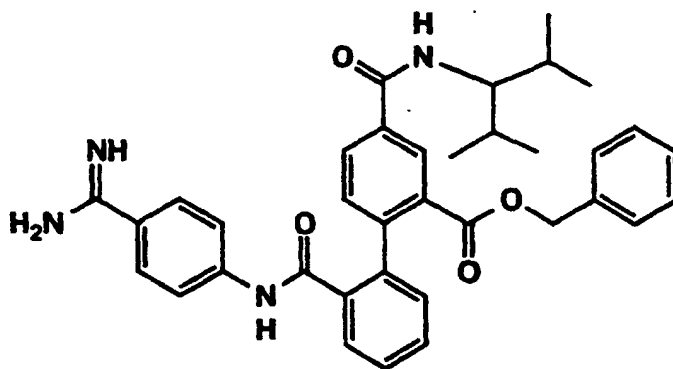
TLC : Rf 0.75 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d_6 -DMSO) : δ 10.65 (1H, s), 9.3-8.8 (3H, br), 8.21 (1H, d, J = 1.5 Hz), 8.13 (1H, d, J = 9.0 Hz), 8.01 (1H, dd, J = 8.0, 1.5 Hz), 7.75 (4H, like s), 7.70 (1H, dd, J = 8.0, 1.5 Hz), 7.6-7.5 (2H, m), 7.38 (1H, d, J = 8.0 Hz), 7.35-7.20 (4H, m), 7.10-7.00 (2H, m), 5.03 (2H, br.s), 3.79 (1H, m), 1.8-1.6 (1H, m), 1.6-1.3 (4H, m), 1.4-1.2 (3H, m), 0.89 (3H, s), 0.83 (3H, s).

Example 40(7)

35 Benzyl 2'-(4-amidinophenylcarbamoyl)-4-(1-isopropyl-2-methylpropyl carbamoyl)-2-biphenylcarboxylate

[0645]



TLC : Rf 0.41 (Chloroform : Methanol : Water = 8 : 2 : 0.2) ;

NMR (200 MHz, CD_3OD) : δ 8.31 (d, J = 2.0 Hz, 1H), 7.96 (dd, J = 8.0, 2.0 Hz, 1H), 7.70-7.59 (m, 5H), 7.55-7.50

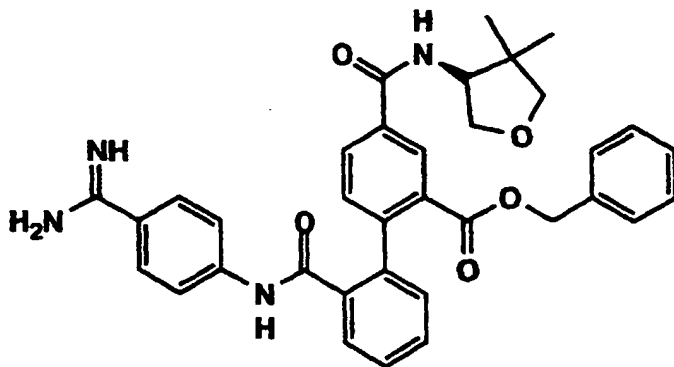
EP 1 078 917 A1

(m, 2H), 7.42 (d, J = 8.0 Hz, 1H), 7.29-7.26 (m, 4H), 7.18-7.13 (m, 2H), 5.14 (s, 2H), 3.72 (t, J = 7.0 Hz, 1H), 1.95 (m, 2H), 0.95 (d, J = 7.0 Hz, 6H), 0.90 (d, J = 7.0 Hz, 6H).

Example 40(8)

Benzyl 2'-[(4-amidinophenylcarbamoyl)-4-[(4, 4-dimethyloxolan-3(S)-yl) carbamoyl]-2-biphenylcarboxylic acid

[0646]



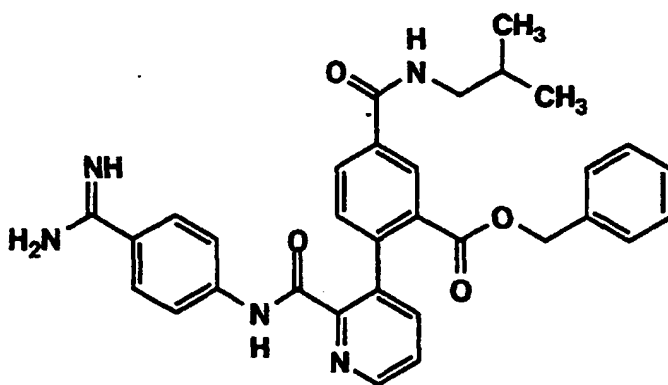
TLC : Rf 0.31 (Chloroform : Methanol : Water = 8 : 2 : 0.1) ;

NMR (200 MHz, CD₃OD) : δ 8.31 (d, J = 1.8 Hz, 1H), 7.98 (dd, J = 8.0, 1.8 Hz, 1H), 7.71-7.59 (m, 6H), 7.59-7.49 (m, 2H), 7.42 (d, J = 8.0 Hz, 1H), 7.28-7.25 (m, 3H), 7.16-7.11 (m, 2H), 5.12 (s, 2H), 4.44 (dd, J = 7.4, 5.4 Hz, 1H), 4.20 (dd, J = 9.2, 7.4 Hz, 1H), 3.72 (dd, J = 9.2, 5.4 Hz, 1H), 3.63-3.53 (m, 2H), 1.16 (s, 3H), 1.02 (s, 3H).

Example 40(9)

Benzyl 2-[2-(4-amidinophenylcarbamoyl)-3-pyridyl]-5-[(2-methylpropyl) carbamoyl]benzoate

[0647]



TLC : Rf 0.62 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

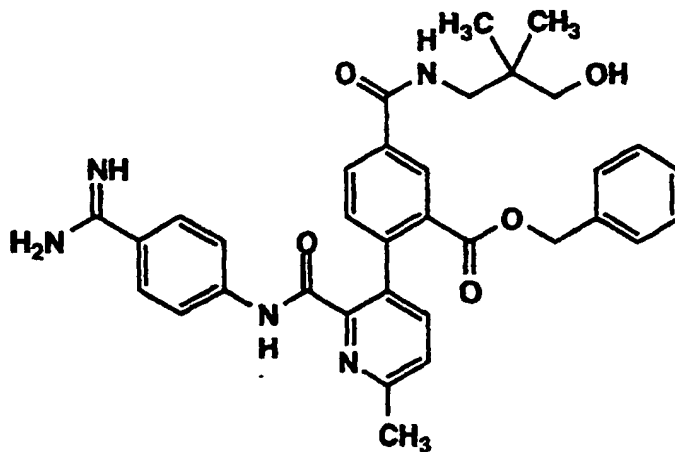
EP 1 078 917 A1

NMR (300 MHz, d_6 -DMSO) : δ 10.98 (s, 1H), 9.4-9.0 (br, 3H), 8.76 (br.t, $J = 6.6$ Hz, 1H), 8.70 (dd, $J = 4.5, 1.8$ Hz, 1H), 8.42 (d, $J = 1.8$ Hz, 1H), 8.11 (dd, $J = 7.8, 1.8$ Hz, 1H), 7.93 (d, $J = 8.7$ Hz, 2H), 7.85-7.75 (m, 1H), 7.79 (d, $J = 8.7$ Hz, 2H), 7.68 (dd, $J = 7.8, 4.5$ Hz, 1H), 7.39 (d, $J = 7.8$ Hz, 1H), 7.3-7.15 (m, 3H), 7.15-7.05 (m, 2H), 5.02 (s, 2H), 3.11 (t, $J = 6.6$ Hz, 2H), 1.87 (like septet, $J = 6.6$ Hz, 1H), 0.90 (d, $J = 6.6$ Hz, 6H).

Example 40(10)

Benzyl 2-[2-(4-amidinophenylcarbamoyl)-6-methyl-3-pyridyl]-5-[(3-hydroxy methyl-2, 2-dimethylpropyl)carbamoyl]benzoate

[0648]



TLC : Rf 0.44 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (300 MHz, CD_3OD) : δ 8.52 (d, $J = 2.0$ Hz, 1H), 8.04 (dd, $J = 8.0, 2.0$ Hz, 1H), 7.85 (d, $J = 9.0$ Hz, 2H), 7.76 (d, $J = 9.0$ Hz, 2H), 7.56 (d, $J = 8.0$ Hz, 1H), 7.43 (d, $J = 8.0$ Hz, 1H), 7.33 (d, $J = 8.0$ Hz, 1H); 7.27-7.16 (m, 3H), 7.09-7.03 (m, 2H), 5.04 (d, $J = 12$ Hz, 1H), 4.98 (d, $J = 12$ Hz, 1H), 3.34 (s, 2H), 3.33-3.30 (m, 2H), 2.64 (s, 3H), 0.96 (s, 6H).

Example 40(11)

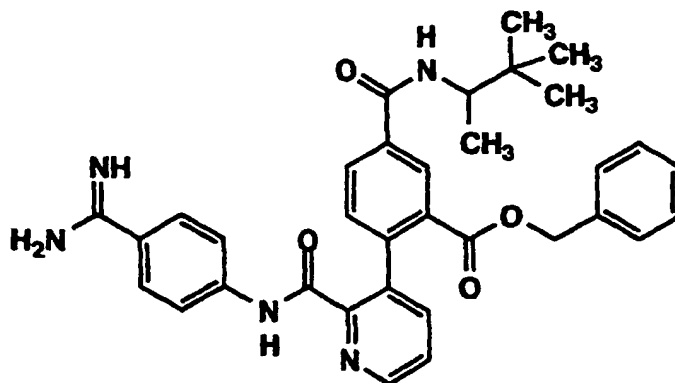
Benzyl 2-[2-(4-amidinophenylcarbamoyl)-3-pyridyl]-5-[(1, 2, 2-trimethylpropyl) carbamoyl]benzoate

5 [0649]

10

15

20



25

TLC : Rf 0.77 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d_6 -DMSO) : δ 10.98 (1H, s), 9.3-8.8 (3H, br), 8.71 (1H, dd, J = 4.2, 1.2 Hz), 8.38 (1H, d, J = 1.2 Hz), 8.27 (1H, br.d, J = 9.0 Hz), 8.09 (1H, dd, J = 7.8, 1.2 Hz), 7.93 (2H, d, J = 8.7 Hz), 7.8-7.75 (3H, m), 7.69 (1H, dd, J = 7.8, 4.2 Hz), 7.38 (1H, d, J = 7.8 Hz), 7.3-7.15 (3H, m), 7.15-7.05 (2H, m), 5.03 (2H, s), 4.00 (1H, m), 1.10 (3H, d, J = 6.4 Hz), 0.92 (9H, s).

30

Example 40(12)

Benzyl 2'-(4-amidinophenylcarbamoyl)-4-[(1(R), 2, 2-trimethylpropyl)carbamoyl]-2-biphenylcarboxylate

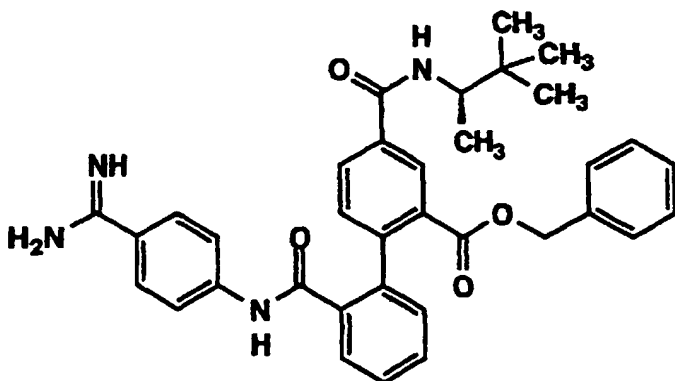
35

[0650]

40

45

50



55

TLC : Rf 0.30 (Chloroform : Methanol : Water = 8 : 2 : 0.1) ;

NMR (200 MHz, CD_3OD) : δ 8.27 (d, J = 2.0 Hz, 1H), 7.94 (dd, J = 8.2, 2.0 Hz, 1H), 7.70-7.58 (m, 5H), 7.55-7.49

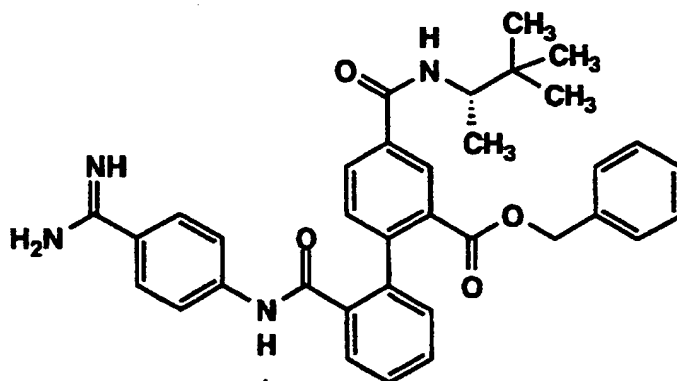
EP 1 078 917 A1

(m, 2H), 7.42 (d, J = 8.0 Hz, 1H), 7.29-7.25 (m, 4H), 7.17-7.12 (m, 2H), 5.12 (s, 2H), 4.10-3.99 (m, 1H), 1.15 (d, J = 7.0 Hz, 3H), 0.95 (s, 9H).

Example 40(13)

Benzy 2'-(4-amidinophenylcarbamoyl)-4-[(1(S), 2, 2-trimethylpropyl)carbamoyl]-2-biphenylcarboxylate

[0651]



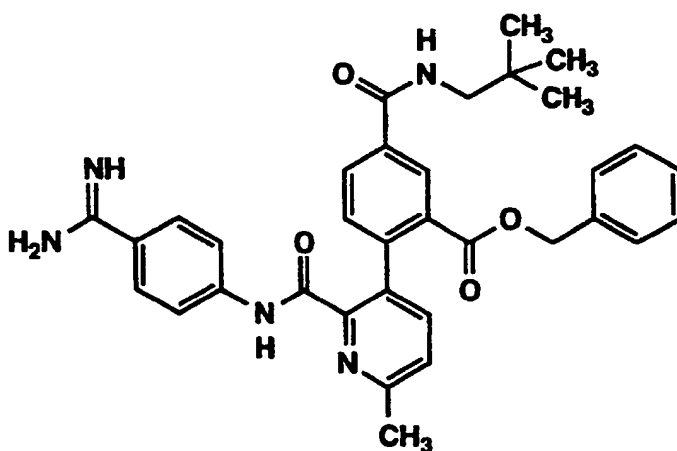
TLC : Rf 0.30 (Chloroform : Methanol : Water = 8 : 2 : 0.1) ;

NMR (200 MHz, CD₃OD) : δ 8.27 (d, J = 2.0 Hz, 1H), 7.94 (dd, J = 8.2, 2.0 Hz, 1H), 7.70-7.58 (m, 5H), 7.55-7.49 (m, 2H), 7.44 (d, J = 8.2 Hz, 1H), 7.29-7.25 (m, 4H), 7.17-7.12 (m, 2H), 5.13 (s, 2H), 4.10-3.99 (m, 1H), 1.15 (d, J = 6.8 Hz, 3H), 0.95 (s, 9H).

Example 40(14)

Benzy 2-[2-(4-amidinophenylcarbamoyl)-6-methyl-3-pyridyl]-5-[(2, 2-dimethylpropyl)carbamoyl]benzoate

[0652]



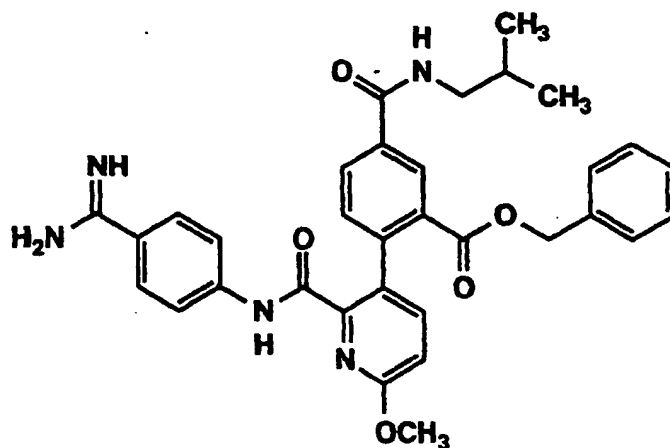
TLC : Rf 0.56 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (300 MHz, CD₃OD) : δ 8.51 (d, J = 2.0 Hz, 1H), 8.03 (dd, J = 8.0, 2.0 Hz, 1H), 7.85 (d, J = 9.0 Hz, 2H), 7.76 (d, J = 9.0 Hz, 2H), 7.55 (d, J = 7.8 Hz, 1H), 7.43 (d, J = 7.8 Hz, 1H), 7.33 (d, J = 8.0 Hz, 1H), 7.28-7.16 (m, 3H), 7.09-7.04 (m, 2H), 5.04 (d, J = 12 Hz, 1H), 4.98 (d, J = 12 Hz, 1H), 3.25 (s, 2H), 2.64 (s, 3H), 0.99 (s, 9H).

Example 40(15)

Benzyl 2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-[(2-methylpropyl)carbamoyl]benzoic acid

[0653]



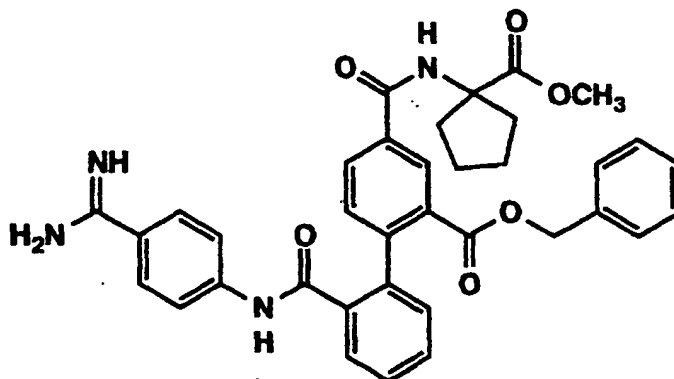
TLC : Rf 0.58 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (300 MHz, CD₃OD) : δ 8.51 (d, J = 2.0 Hz, 1H), 8.02 (dd, J = 8.0, 2.0 Hz, 1H), 7.83 (d, J = 9.0 Hz, 2H), 7.77 (d, J = 9.0 Hz, 2H), 7.54 (d, J = 8.4 Hz, 1H), 7.31 (d, J = 8.0 Hz, 1H), 7.28-7.16 (m, 3H), 7.10-7.04 (m, 2H), 6.98 (d, J = 8.4 Hz, 1H), 5.07 (brd, J = 12 Hz, 1H), 4.98 (brd, J = 12 Hz, 1H), 4.06 (s, 3H), 3.23 (d, J = 6.8 Hz, 2H), 2.03-1.88 (m, 1H), 0.98 (d, J = 6.8 Hz, 6H).

Example 40(16)

Benzyl 2'-(4-amidinophenylcarbamoyl)-4-(1-methoxycarbonylcyclopentyl carbamoyl)-2-biphenylcarboxylate

5 [0654]

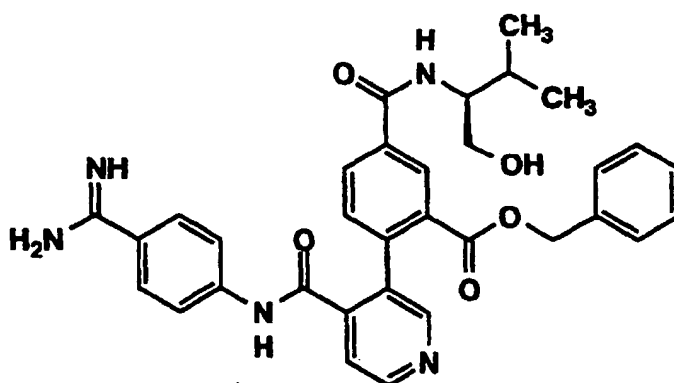


25 TLC : Rf 0.40 (Chloroform : Methanol : Water = 8 : 2 : 0.1) ;
 NMR (200 MHz, CD₃OD) : δ 8.30 (d, J = 1.8 Hz, 1H), 7.97 (dd, J = 8.0, 1.8 Hz, 1H), 7.70-7.62 (m, 5H), 7.55-7.48 (m, 2H), 7.41 (d, J = 7.6 Hz, 1H), 7.28-7.22 (m, 4H), 7.17-7.12 (m, 2H), 5.12 (s, 2H), 3.68 (s, 3H), 2.36-2.21 (m, 2H), 2.13-2.00 (m, 2H), 1.86-1.75 (m, 4H).

30 Example 40(17)

Benzyl 2-[4-(4-amidinophenylcarbamoyl)-3-pyridyl]-5-[(1(S)-hydroxymethyl-2-methylpropyl)carbamoyl]benzoate

35 [0655]



50

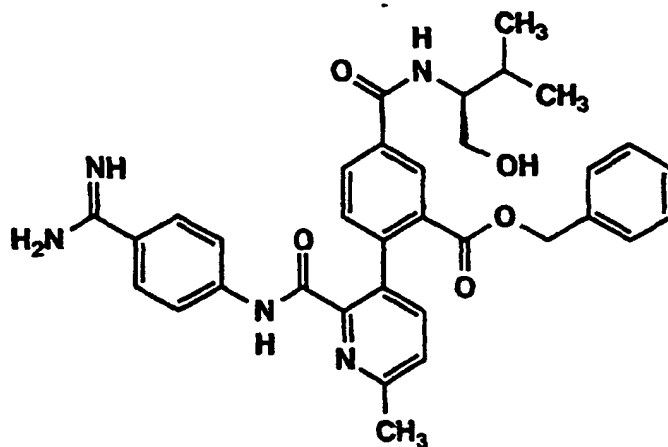
55 TLC : Rf 0.22 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;
 NMR (300 MHz, CD₃OD) : δ 8.63 (d, J = 5.1 Hz, 1H), 8.50 (d, J = 1.0 Hz, 1H), 8.45 (d, J = 2.0 Hz, 1H), 8.06 (dd, J = 8.0, 2.0 Hz, 1H), 7.71 (d, J = 9.0 Hz, 2H), 7.67 (d, J = 9.0 Hz, 2H), 7.60 (dd, J = 5.1, 1.0 Hz, 1H), 7.48 (d, J = 8.0 Hz, 1H), 7.30-7.26 (m, 3H), 7.20-7.16 (m, 2H), 5.14 (brd, J = 12 Hz, 1H), 5.09 (brd, J = 12 Hz, 1H), 3.91 (ddd, J = 6.9, 6.6, 4.2 Hz, 1H), 3.73 (dd, J = 11.4, 4.2 Hz, 1H), 3.65 (dd, J = 11.4, 6.6 Hz, 1H), 2.05-1.94 (m, 1H), 1.00 (d, J

= 6.6 Hz, 3H), 0.96 (d, J = 6.9 Hz, 3H).

Example 40(18)

- 5 Benzyl 2-[2-(4-amidinophenylcarbamoyl)-6-methyl-3-pyridyl]-5-[(1(S)-hydroxymethyl-2-methylpropyl)carbamoyl]benzoate

[0656]



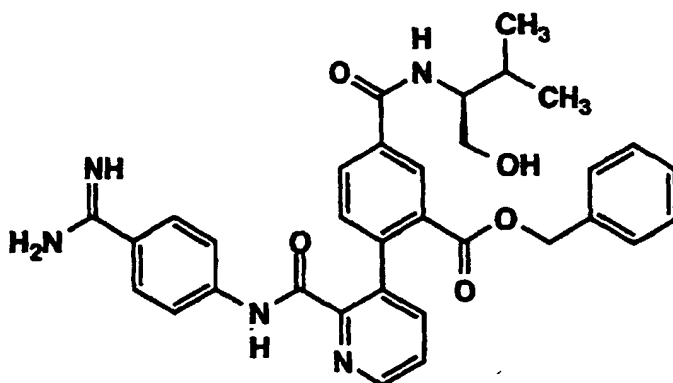
TLC : Rf 0.43 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (300 MHz, CD₃OD) : δ 8.54 (d, J = 2.0 Hz, 1H), 8.05 (dd, J = 8.0, 2.0 Hz, 1H), 7.85 (d, J = 9.0 Hz, 2H), 7.76 (d, J = 9.0 Hz, 2H), 7.55 (d, J = 8.0 Hz, 1H), 7.43 (d, J = 8.0 Hz, 1H), 7.32 (d, J = 8.0 Hz, 1H), 7.28-7.16 (m, 3H), 7.10-7.03 (m, 2H), 5.04 (brd, J = 12 Hz, 1H), 4.98 (brd, J = 12 Hz, 1H), 3.96 (ddd, J = 6.9, 6.6, 4.2 Hz, 1H), 3.76 (dd, J = 11.4, 4.2 Hz, 1H), 3.70 (dd, J = 11.4, 6.6 Hz, 1H), 2.64 (s, 3H), 2.09-1.93 (m, 1H), 1.03 (d, J = 6.6 Hz, 3H), 1.00 (d, J = 6.9 Hz, 3H).

Example 40(19)

Benzyl 2-[2-(4-amidinophenylcarbamoyl)-3-pyridyl]-5-[(1(S)-hydroxymethyl-2-methylpropyl)carbamoyl]benzoate

[0657]



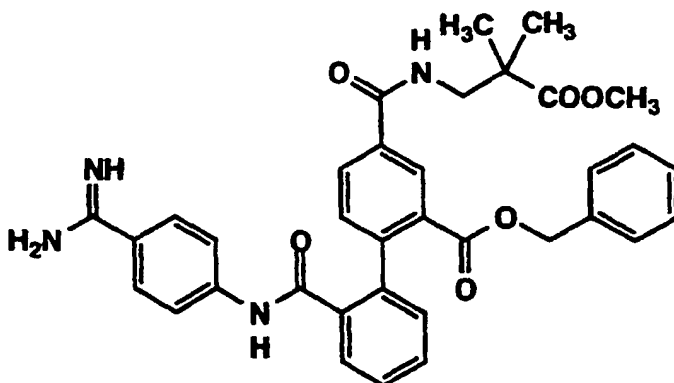
TLC : Rf 0.83 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d_6 -DMSO) : δ 10.97 (s, 1H), 9.3-8.8 (br, 3H), 8.71 (dd, J = 4.4, 2.1 Hz, 1H), 8.42 (d, J = 2.1 Hz, 1H), 8.28 (d, J = 9.6 Hz, 1H), 8.13 (dd, J = 8.0, 2.1 Hz, 1H), 7.94 (d, J = 9.0 Hz, 2H), 7.77 (d, J = 9.0 Hz, 2H), 7.8-7.7 (m, 1H), 7.68 (dd, J = 8.0, 4.4 Hz, 1H), 7.38 (d, J = 8.0 Hz, 1H), 7.3-7.2 (m, 3H), 7.15-7.0 (m, 2H), 5.02 (s, 2H), 4.61 (t, J = 5.5 Hz, 1H), 3.83 (m, 1H), 3.53 (t, J = 5.5 Hz, 2H), 1.90 (like sextet, J = 6.6 Hz, 1H), 0.92 (d, J = 6.6 Hz, 3H), 0.88 (d, J = 6.6 Hz, 3H).

Example 40(20)

Benzyl 2'-(4-amidinophenylcarbamoyl)-4-[(2-methoxycarbonyl-2,2-dimethyl ethyl)carbamoyl]-2-biphenylcarboxylate

[0658]



TLC : Rf 0.49 (Chloroform : Methanol : Water = 8 : 2 : 0.1) ;

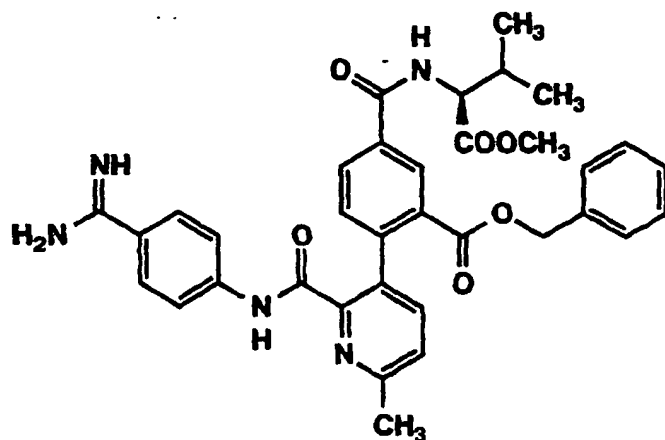
NMR (200 MHz, $CDCl_3$) : δ 8.27 (d, J = 2.0 Hz, 1H), 7.95 (dd, J = 8.0, 2.0 Hz, 1H), 7.70-7.58 (m, 5H), 7.55-7.49 (m,

2H), 7.42 (d, J = 8.0 Hz, 1H), 7.30-7.22 (m, 4H), 7.17-7.12 (m, 2H), 5.12 (s, 2H), 3.64 (s, 3H), 3.52 (s, 2H), 1.21 (s, 6H).

Example 40(21)

Benzyl 2-[2-(4-amidinophenylcarbamoyl)-6-methyl-3-pyridyl]-5-[(1(S)-methoxycarbonyl-2-methylpropyl)carbamoyl]benzoate

[0659]



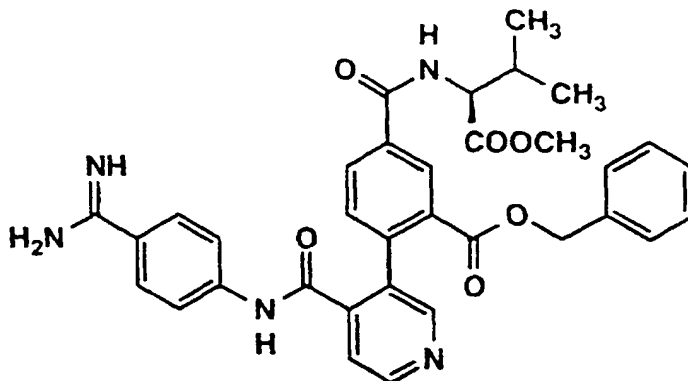
TLC : Rf 0.71 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (300 MHz, CD₃OD) : δ 8.52 (d, J = 2.0 Hz, 1H), 8.05 (dd, J = 8.0, 2.0 Hz, 1H), 7.85 (d, J = 9.0 Hz, 2H), 7.76 (d, J = 9.0 Hz, 2H), 7.56 (d, J = 8.0 Hz, 1H), 7.43 (d, J = 8.0 Hz, 1H), 7.33 (d, J = 8.0 Hz, 1H), 7.26-7.16 (m, 3H), 7.10-7.06 (m, 2H), 5.04 (brd, J = 12 Hz, 1H), 4.98 (brd, J = 12 Hz, 1H), 4.52 (d, J = 6.9 Hz, 1H), 3.76 (s, 3H), 2.64 (s, 3H), 2.34-2.23 (m, 1H), 1.06 (d, J = 6.3 Hz, 3H), 1.04 (d, J = 6.6 Hz, 3H).

Example 40(22)

Benzyl 2-[4-(4-amidinophenylcarbamoyl)-3-pyridyl]-5-[(1(S)-methoxycarbonyl-2-methylpropyl)carbamoyl]benzoate

[0660]



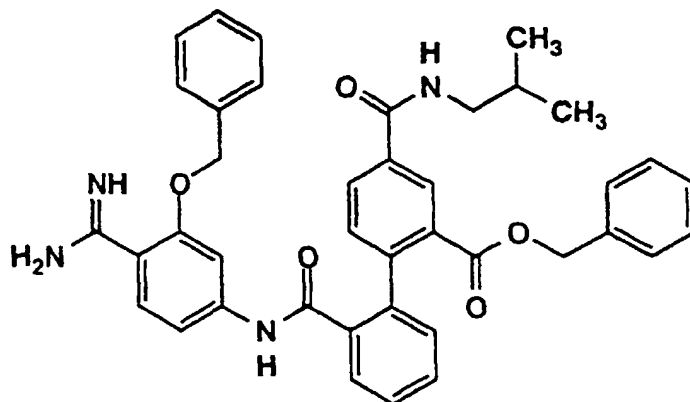
TLC : Rf 0.63 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (300 MHz, CD₃OD) : δ 8.64 (d, J = 5.0 Hz, 1H), 8.51 (s, 1H), 8.44 (d, J = 2.0 Hz, 1H), 8.06 (dd, J = 8.0, 2.0 Hz, 1H), 7.71 (d, J = 9.0 Hz, 2H), 7.67 (d, J = 9.0 Hz, 2H), 7.60 (d, J = 5.0 Hz, 1H), 7.49 (d, J = 8.0 Hz, 1H), 7.30-7.24 (m, 3H), 7.20-7.14 (m, 2H), 5.14 (brd, J = 12 Hz, 1H), 5.10 (brd, J = 12 Hz, 1H), 4.47 (d, J = 7.0 Hz, 1H), 3.74 (s, 3H), 2.31-2.19 (m, 1H), 1.02 (d, J = 6.6 Hz, 3H), 1.00 (d, J = 6.9 Hz, 3H).

Example 40(23)

Benzyl 2'-(4-amidino-3-benzyloxyphenylcarbamoyl)-4-2-methylpropylcarbamoyl)-2-biphenylcarboxylate

[0661]



TLC : Rf 0.31 (Chloroform : Methanol : Water = 8 : 2 : 0.2) ;

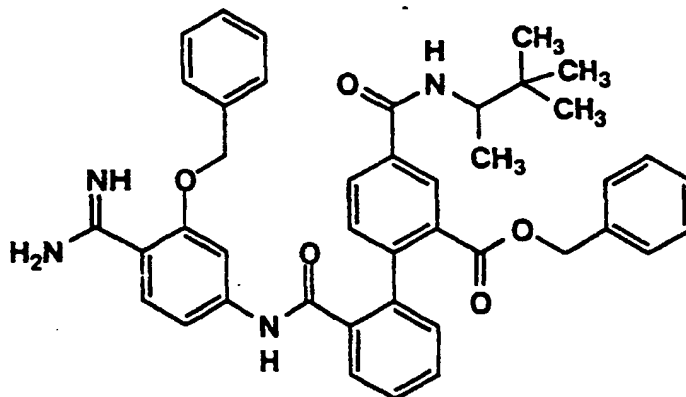
NMR (200 MHz, CD₃OD) : δ 8.34 (d, J = 2.0 Hz, 1H), 7.98 (dd, J = 8.0, 2.0 Hz, 1H), 7.67 (dd, J = 8.0, 2.0 Hz, 1H),

7.55-7.24 (m, 14H), 7.17-7.12 (m, 2H), 7.01 (dd, $J = 8.0, 2.0$ Hz, 1H), 5.12 (s, 2H), 5.10 (s, 2H), 3.18 (d, $J = 7.0$ Hz, 2H), 1.91 (m, 1H), 0.95 (d, $J = 6.6$ Hz, 6H).

Example 40(24)

Benzyl 2'-(4-amidino-3-benzyloxyphenylcarbamoyl)-4-(1,2,2-trimethylpropyl carbamoyl)-2-biphenylcarboxylate

[0662]



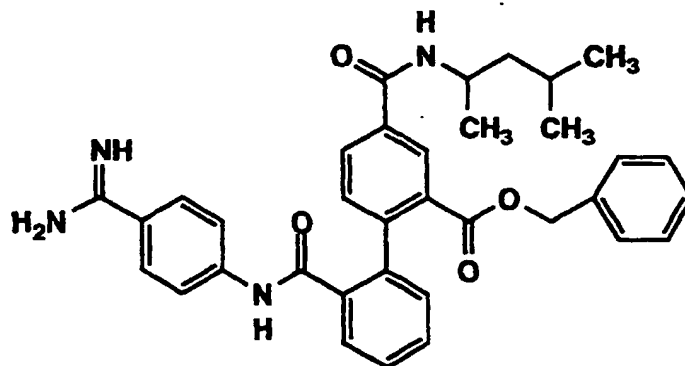
TLC : Rf 0.38 (Chloroform : Methanol : Water = 8 : 2 : 0.2) ;

NMR (300 MHz, CD_3OD) : δ 8.31 (d, $J = 2.0$ Hz, 1H), 8.17 (br.d, $J = 9.0$ Hz, 1H), 7.95 (dd, $J = 8.0, 2.0$ Hz, 1H), 7.66 (dd, $J = 8.0, 2.0$ Hz, 1H), 7.58 (d, $J = 2.0$ Hz, 1H), 7.54-7.50 (m, 2H), 7.46 (d, $J = 8.0$ Hz, 1H), 7.43-7.31 (m, 5H), 7.29-7.24 (m, 4H), 7.15-7.12 (m, 2H), 7.02 (d, $J = 8.0$ Hz, 1H), 5.10 (s, 4H), 4.06 (m, 1H), 1.16 (d, $J = 7.0$ Hz, 3H), 0.96 (s, 9H).

Example 40(25)

Benzyl 2'-(4-amidinophenylcarbamoyl)-4-(1, 3-dimethylbutylcarbamoyl)-2-biphenylcarboxylate

[0663]



EP 1 078 917 A1

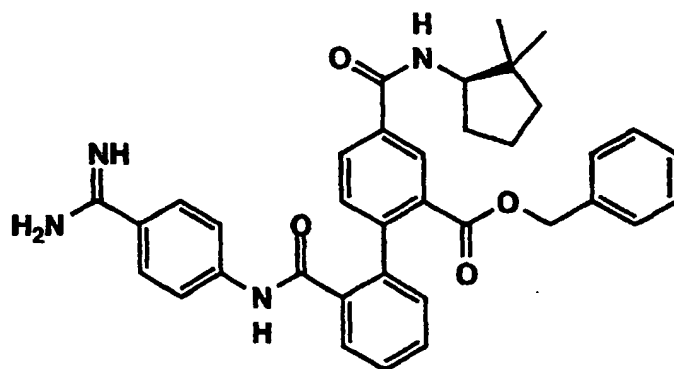
TLC : Rf 0.30 (Chloroform : Ethyl acetate: Water = 8 : 2 : 0.2) ;

NMR (300 MHz, CD₃OD) : δ 8.30 (d, J = 2.0 Hz, 1H), 7.95 (dd, J = 8.1, 2.0 Hz, 1H), 7.69-7.65 (m, 4H), 7.62-7.59 (m, 2H), 7.52 (m, 2H), 7.41 (d, J = 8.1 Hz, 1H), 7.28-7.26 (m, 3H), 7.17-7.14 (m, 2H), 5.13 (s, 2H), 4.22 (m, 1H), 1.70-1.52 (m, 2H), 1.25 (m, 1H), 1.19 (d, J = 6.6 Hz, 3H), 0.93 (d, J = 6.6 Hz, 6H).

Example 40(26)

Benzyl 2'-(4-amidinophenylcarbamoyl)-4-(2, 2-dimethyl-1(R)-cyclopentyl carbamoyl)-2-biphenylcarboxylate

[0664]



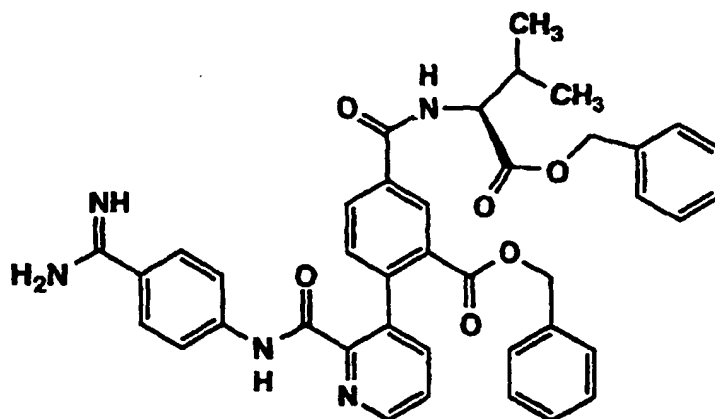
TLC : Rf 0.50 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (300 MHz, CD₃OD) : δ 8.28 (d, J = 1.8 Hz, 1H), 7.95 (dd, J = 7.8, 1.8 Hz, 1H), 7.70-7.58 (m, 5H), 7.53 (td, J = 6.0, 1.8 Hz, 1H), 7.50 (td, J = 6.0, 1.8 Hz, 1H), 7.41 (d, J = 7.8 Hz, 1H), 7.30-7.22 (m, 4H), 7.18-7.12 (m, 2H), 5.12 (s, 2H), 4.17 (q, J = 7.8 Hz, 1H), 2.08-1.98 (m, 1H), 1.80-1.52 (m, 5H), 1.05 (s, 3H), 0.93 (s, 3H).

Example 40(27)

Benzyl 2-[2-(4-amidinophenylcarbamoyl)-3-pyridyl]-5-[(1(S)-carboxy-2-methylpropyl)carbamoyl]benzoate

[0665]



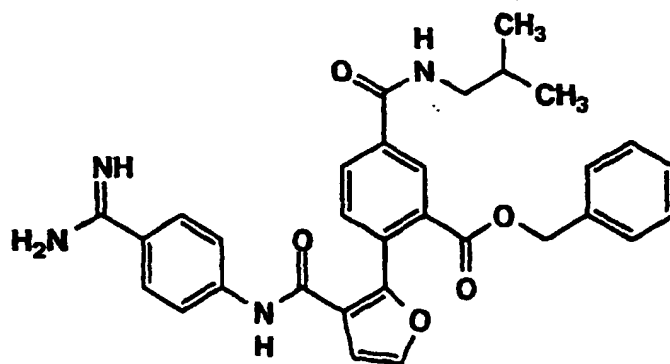
TLC : Rf 0.73 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d_6 -DMSO) : δ 10.40 (1H, br.s), 9.10 (3H, br.s), 8.97 (1H, br.s, J = 7.5 Hz), 8.71 (1H, dd, J = 4.5, 1.5 Hz), 8.43 (1H, d, J = 1.5 Hz), 8.14 (1H, dd, J = 8.0, 1.5 Hz), 7.94 (2H, d, J = 9.0 Hz), 7.78 (2H, d, J = 9.0 Hz), 7.8-7.7 (1H, m), 7.69 (1H, dd, J = 7.5, 4.5 Hz), 7.41 (1H, d, J = 8.0 Hz), 7.4-7.3 (5H, m), 7.25-7.15 (3H, m), 7.15-7.05 (2H, m), 5.20 (1H, d, J = 12.6 Hz), 5.14 (1H, d, J = 12.6 Hz), 5.03 (2H, s), 4.37 (1H, t, J = 7.5 Hz), 2.23 (1H, m), 0.99 (3H, d, J = 6.6 Hz), 0.94 (3H, d, J = 6.6 Hz).

Example 40(28)

Benzyl 2-[3-(4-amidinophenylcarbamoyl)-2-furyl]-5-(2-methylpropylcarbamoyl) benzoate

[0666]



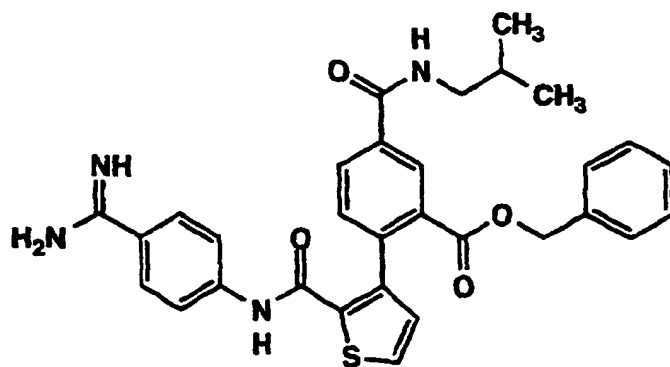
TLC : Rf 0.61 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR(300 MHz, DMSO- d_6) : δ 8.38 (d, J = 2.0 Hz, 1H), 8.04 (dd, J = 8.0, 2.0 Hz, 1H), 7.85 (d, J = 9.3 Hz, 2H), 7.76 (d, J = 9.3 Hz, 2H), 7.70 (d, J = 8.0 Hz, 1H), 7.60 (d, J = 2.1 Hz, 1H), 7.27 (s, 5H), 7.02 (d, J = 2.1 Hz, 1H), 5.15 (s, 2H), 3.21 (d, J = 6.9 Hz, 2H), 2.01-1.87 (m, 1H), 0.97 (d, J = 6.6 Hz, 6H).

Example 40(29)

Benzyl 2-[2-(4-amidinophenylcarbamoyl)-3-thienyl]-5-(2-methylpropyl carbamoyl)benzoate

[0667]



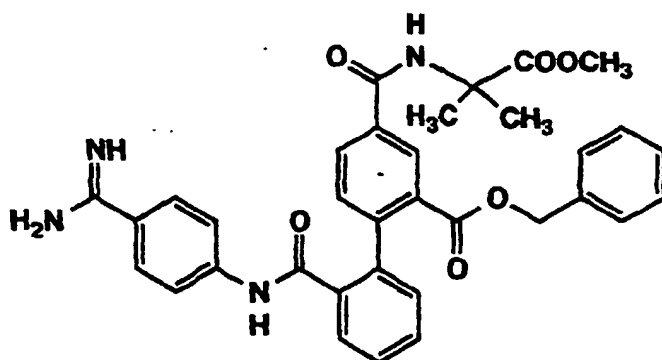
TLC : Rf 0.71 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (300 MHz, DMSO- d_6) : δ 8.35 (d, J = 1.8 Hz, 1H), 8.01 (dd, J = 8.0, 1.8 Hz, 1H), 7.70 (d, J = 9.0 Hz, 2H), 7.67 (d, J = 5.0 Hz, 1H), 7.60 (d, J = 9.0 Hz, 2H), 7.49 (d, J = 8.0 Hz, 1H), 7.29-7.17 (m, 5H), 7.06 (d, J = 5.0 Hz, 1H), 5.12 (s, 2H), 3.20 (d, J = 6.9 Hz, 2H), 2.00-1.86 (m, 1H), 0.96 (d, J = 6.6 Hz, 6H).

Example 40(30)

Benzyl 2'-(4-amidinophenylcarbamoyl)-4-[(1-methoxycarbonyl-1-methylethyl) carbamoyl]-2-biphenylcarboxylate

[0668]



TLC : Rf 0.40 (Chloroform : Ethyl acetate: Water = 8 : 2 : 0.2) ;

NMR(300 MHz, CD $_3$ OD) : δ 8.32 (d, J = 2.0 Hz, 1H), 7.96 (dd, J = 6.9, 2.0 Hz, 2H), 7.68-7.66 (m, 3H), 7.62-7.58 (m, 2H), 7.53-7.50 (m, 2H), 7.42 (d, J = 7.8 Hz, 1H), 7.28-7.25 (m, 3H), 7.17-7.13 (m, 2H), 5.13 (s, 2H), 3.70 (s, 3H), 1.55 (s, 6H).

Example 40(31)

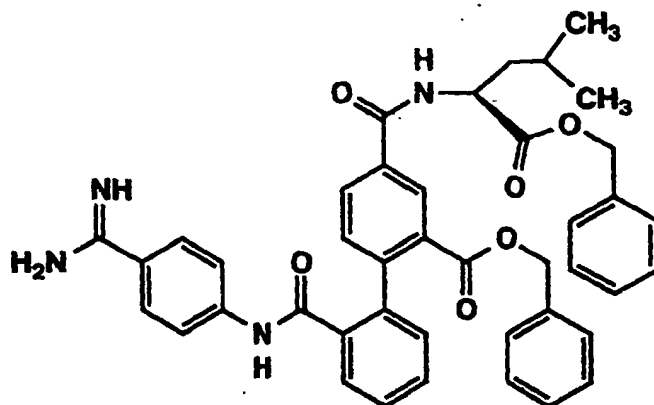
Benzyl 2'-[4-amidinophenylcarbamoyl]-4-(1(S)-carboxy-3-methylbutyl carbamoyl)-2-biphenylcarboxylate

5 [0669]

10

15

20



25

TLC : Rf 0.40 (Chloroform : Ethyl acetate: Water = 8 : 2 : 0.2) ;

NMR (300 MHz, DMSO-d₆) : δ 10.64 (s, 1H), 9.12 (br, 1H), 9.01 (d, J = 7.5 Hz, 1H), 8.87 (br, 1H), 8.29 (d, J = 2.1 Hz, 1H), 8.07 (dd, J = 8.1, 2.1 Hz, 1H), 7.78-7.59 (m, 4H), 7.59 (m, 1H), 7.55 (m, 1H), 7.44 (d, J = 8.1 Hz, 1H), 7.35-7.23 (m, 6H), 7.07-7.03 (m, 2H), 5.14 (s, 2H), 5.05 (s, 2H), 4.54 (m, 1H), 1.84-1.50 (m, 3H), 0.92 (d, J = 6.3 Hz, 3H), 0.87 (d, J = 6.0 Hz, 3H).

30

Example 40(32)

Benzyl 2-[2-(4-amidinophenylcarbamoyl)-3-pyridyl]-5-(2,2-dimethylpropyl carbamoyl)benzoate

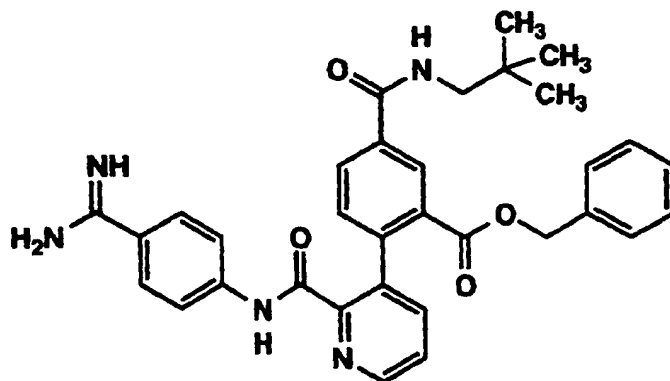
35

[0670]

40

45

50



55

TLC : Rf 0.80 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d₆-DMSO) : δ 10.98 (br.s, 1H), 9.11 (br.s, 3H), 8.71 (dd, J = 4.5, 1.5 Hz, 1H), 8.65 (t, J = 6.3 Hz, 1H), 8.42

EP 1 078 917 A1

(d, J = 1.5 Hz, 1H), 8.11 (dd, J = 8.0, 1.5 Hz, 1H), 7.93 (d, J = 9.0 Hz, 2H), 7.78 (d, J = 9.0 Hz, 2H), 7.85-7.75 (m, 1H), 7.68 (dd, J = 8.0, 4.5 Hz, 1H), 7.39 (d, J = 8.0 Hz, 1H), 7.25-7.15 (m, 3H), 7.15-7.05 (m, 2H), 5.03 (s, 2H), 3.14 (d, J = 6.3 Hz, 2H), 0.91 (s, 9H).

5 Example 40(33)

Benzyl 2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-(2, 2-dimethylpropylcarbamoyl)benzoate

[0671]

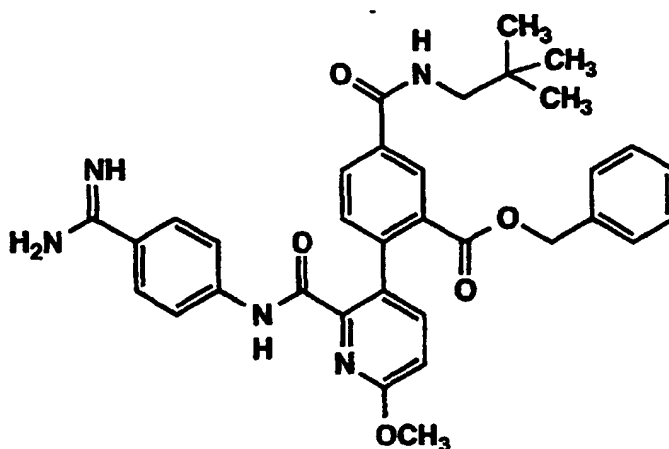
10

15

20

25

30



35

TLC : Rf 0.72 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (300 MHz, DMSO-d₆) : δ 8.50 (d, J = 2.0 Hz, 1H), 8.01 (dd, J = 8.0, 2.0 Hz, 1H), 7.83 (d, J = 9.3 Hz, 2H), 7.77 (d, J = 9.3 Hz, 2H), 7.55 (d, J = 8.3 Hz, 1H), 7.32 (d, J = 8.0 Hz, 1H), 7.26-7.16 (m, 3H), 7.10-7.05 (m, 2H), 6.98 (d, J = 8.3 Hz, 1H), 5.07 (brd, J = 12 Hz, 1H), 4.98 (brd, J = 12 Hz, 1H), 4.06 (s, 3H), 3.25 (s, 2H), 0.99 (s, 9H).

Example 40(34)

Benzyl 2'-(4-amidinophenylcarbamoyl)-4-(2, 2-dimethyl-1(S)-cyclopentyl carbamoyl)-2-biphenylcarboxylate

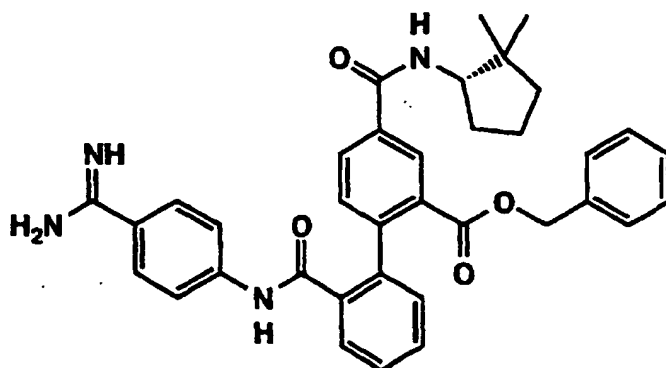
40

[0672]

45

50

55



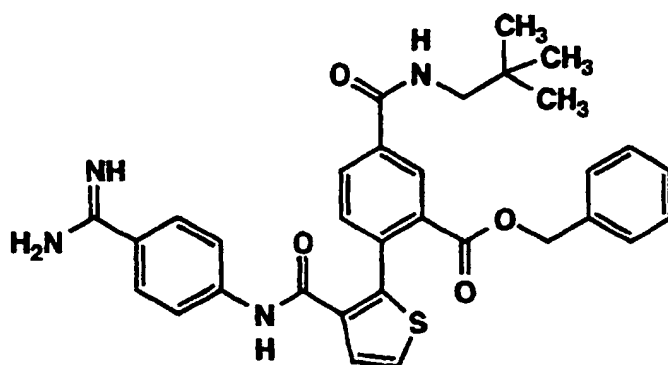
TLC : Rf 0.5 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (300 MHz, CD₃OD) : δ 8.28 (d, J = 1.8 Hz, 1H), 7.95 (dd, J = 7.8, 1.8 Hz, 1H), 7.70-7.58 (m, 5H), 7.53 (td, J = 6.0, 1.8 Hz, 1H), 7.50 (td, J = 6.0, 1.8 Hz, 1H), 7.41 (d, J = 7.8 Hz, 1H), 7.30-7.22 (m, 4H), 7.18-7.12 (m, 2H), 5.12 (s, 2H), 4.17 (q, J = 7.8 Hz, 1H), 2.08-1.98 (m, 1H), 1.80-1.52 (m, 5H), 1.05 (s, 3H), 0.93 (s, 3H).

Example 40(35)

Benzyl 2-[3-(4-amidinophenylcarbamoyl)-2-thienyl]-5-(2, 2-dimethylpropyl carbamoyl)benzoate

[0673]



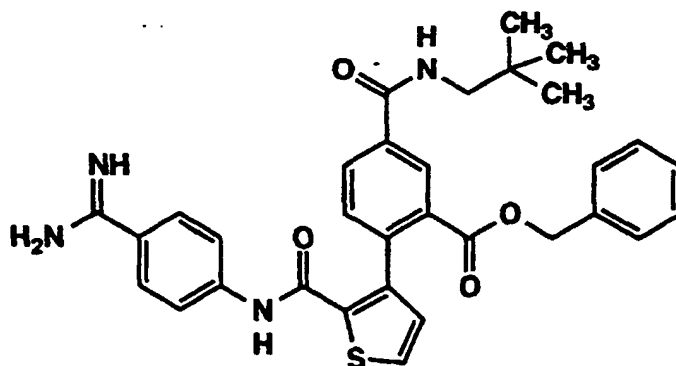
TLC : Rf 0.51 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (300 MHz, d₆-DMSO) : δ 10.38 (s, 1H), 9.3-8.9 (br, 3H), 8.65 (br.t, J = 6.3 Hz, 1H), 8.29 (d, J = 1.8 Hz, 1H), 8.06 (dd, J = 8.1, 1.8 Hz, 1H), 7.83 (d, J = 9.0 Hz, 2H), 7.77 (d, J = 9.0 Hz, 2H), 7.73 (d, J = 5.4 Hz, 1H), 7.68 (d, J = 5.4 Hz, 1H), 7.54 (d, J = 8.1 Hz, 1H), 7.3-7.2 (m, 3H), 7.2-7.1 (m, 2H), 5.06 (s, 2H), 3.12 (d, J = 6.3 Hz, 2H), 0.90 (s, 9H).

Example 40(36)

Benzyl 2-(2-(4-amidinophenylcarbamoyl)-3-thienyl)-5-(2, 2-dimethylpropyl carbamoyl)benzoate

[0674]



EP 1 078 917 A1

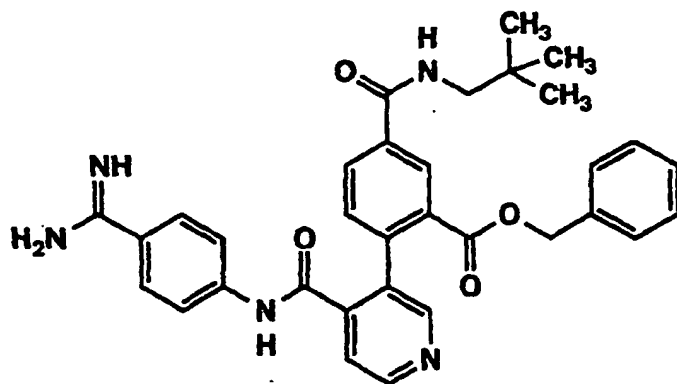
TLC : Rf 0.44 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (200 MHz, d₆-DMSO) : δ 10.29 (s, 1H), 9.07 (br.s, 3H), 8.59 (br.t, J = 6.2 Hz, 1H), 8.28 (d, J = 1.8 Hz, 1H), 8.06 (dd, J = 8.0, 1.8 Hz, 1H), 7.85 (d, J = 5.2 Hz, 1H), 7.77 (d, J = 9.6 Hz, 2H), 7.71 (d, J = 9.6 Hz, 2H), 7.47 (d, J = 8.0 Hz, 1H), 7.3-7.2 (m, 3H), 7.2-7.1 (m, 2H), 7.15 (d, J = 5.2 Hz, 1H), 5.08 (s, 2H), 3.11 (d, J = 6.2 Hz, 2H), 0.89 (s, 9H).

Example 40(37)

Benzyl 2-[4-(4-amidinophenylcarbamoyl)-3-pyridyl]-5-(2, 2-dimethylpropyl carbamoyl)benzoate

[0675]



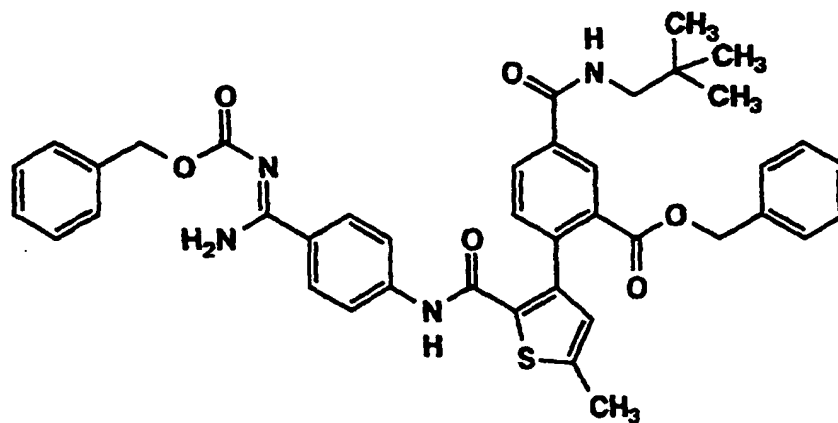
TLC : Rf 0.60 (Chloroform : Ethyl acetate: Water = 7 : 3 : 0.3) ;

NMR (200 MHz, DMSO-d₆) : δ 10.94 (brs, 1H), 9.24 (br, 2H), 9.02 (br, 2H), 8.76 (d, J = 4.4 Hz, 1H), 8.16-8.57 (m, 2H), 8.35 (s, 1H), 8.10 (d, J = 7.4 Hz, 1H), 7.77 (s, 3H), 7.69 (d, J = 4.4 Hz, 1H), 7.49 (d, J = 8.0 Hz, 1H), 7.28 (m, 3H), 7.13 (m, 2H), 5.07 (s, 2H), 4.11 (d, J = 5.0 Hz, 1H), 3.17 (d, J = 4.8 Hz, 2H), 0.90 (s, 9H).

Example 40(38)

Benzyl 2-[2-(4-benzyloxycarbonylamidinophenylcarbamoyl)-5-methyl-3-thienyl]-5-(2, 2-dimethylpropylcarbamoyl)benzoate

[0676]



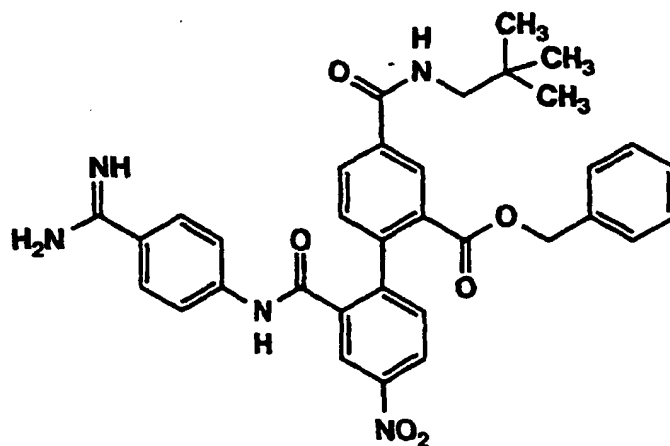
TLC : Rf 0.62 (Chloroform : Methanol = 10 : 1) ;

NMR (300 MHz, CDCl₃) : δ 10.0-9.20 (br, 1H), 8.35 (d, J = 1.8 Hz, 1H), 7.95 (dd, J = 8.0, 1.8 Hz, 1H), 7.71 (d, J = 9.0 Hz, 2H), 7.60 (s, 1H), 7.45-7.40 (m, 3H), 7.40-7.25 (m, 7H), 7.25-7.15 (m, 3H), 6.53 (s, 1H), 6.60-6.00 (br, 1H), 6.28 (br.t, J = 6.0 Hz, 1H), 5.20 (s, 2H), 5.18 (s, 2H), 3.30 (d, J = 6.0 Hz, 2H), 2.47 (s, 3H), 0.99 (s, 9H).

Example 40(39)

Benzyl 2'-(4-amidinophenylcarbamoyl)-4'-nitro-4-(2, 2-dimethylpropyl carbamoyl)-2-biphenylcarboxylate

[0677]



EP 1 078 917 A1

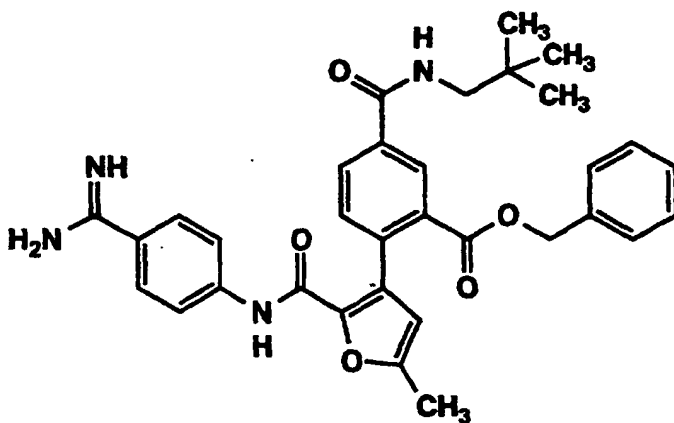
TLC : Rf 0.40 (Chloroform : Methanol : Water = 8 : 2 : 0.2) ;

NMR (300 MHz, CD₃OD) : δ 8.45 (d, J = 2.0 Hz, 1H), 8.37 (d, J = 2.0 Hz, 1H), 8.23 (dd, J = 8.0, 2.0 Hz, 1H), 8.02 (dd, J = 8.0, 2.0 Hz, 1H), 7.72 (d, J = 9.0 Hz, 2H), 7.68 (d, J = 9.0 Hz, 2H), 7.48 (d, J = 8.0 Hz, 1H), 7.43 (d, J = 8.0 Hz, 1H), 7.23-7.19 (m, 3H), 7.14-7.11 (m, 2H), 5.10 (d, J = 12.0 Hz, 1H), 5.05 (d, J = 12.0 Hz, 1H), 3.22 (s, 2H), 0.97 (s, 9H).

Example 40(40)

Benzy 2-[2-(4-amidinophenylcarbamoyl)-5-methyl-3-furyl]-5-(2, 2-dimethylpropylcarbamoyl)benzoate

[0678]



TLC : Rf 0.61 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (200 MHz, d₆-DMSO) : δ 13.38 (br.s, 1H), 9.09 (br.s, 3H), 8.60 (t, J = 6.2 Hz, 1H), 8.34 (d, J = 1.6 Hz, 1H), 8.03 (dd, J = 8.0, 1.6 Hz, 1H), 7.92 (d, J = 8.8 Hz, 2H), 7.78 (d, J = 8.8 Hz, 2H), 7.48 (d, J = 8.0 Hz, 1H), 7.4-7.2 (m, 5H), 6.42 (s, 1H), 5.11 (s, 2H), 3.13 (d, J = 6.2 Hz, 2H), 2.42 (s, 3H), 0.91 (s, 9H).

Example 40(41)

Benzyl 2-[4-(4-amidinophenylcarbamoyl)-2-methyl-pyrimidin-5-yl]-5-(2, 2-dimethylpropylcarbamoyl)benzoate

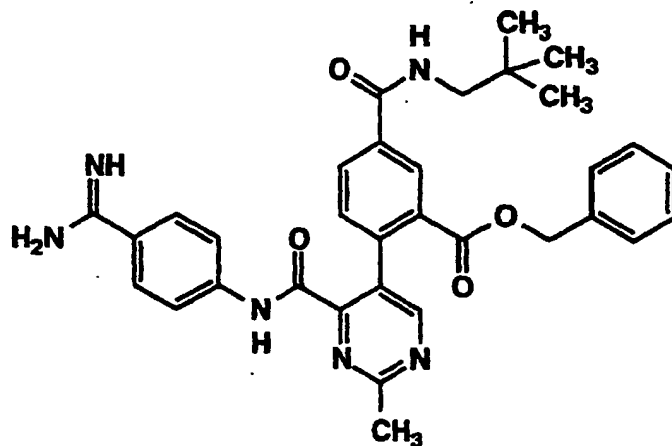
5 [0679]

10

15

20

25



30

TLC : Rf 0.71 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (300 MHz, CD₃OD) : δ 8.64 (s, 1H), 8.57 (d, J = 2.0 Hz, 1H), 8.08 (dd, J = 8.0, 2.0 Hz, 1H), 7.89 (d, J = 9.0 Hz, 2H), 7.78 (d, J = 9.0 Hz, 2H), 7.40 (d, J = 8.0 Hz, 1H), 7.28-7.19 (m, 3H), 7.16-7.10 (m, 2H), 5.08 (brd, J = 12 Hz, 1H), 5.02 (brd, J = 12 Hz, 1H), 3.25 (s, 2H), 2.80 (s, 3H), 0.99 (s, 9H).

Example 40(42)

35 Benzyl 2-[2-(4-amidinophenylcarbamoyl)-6-methyl-3-pyridyl]-5-(1(S)-morpholinocarbonyl-3-methylbutylcarbamoyl)benzoate

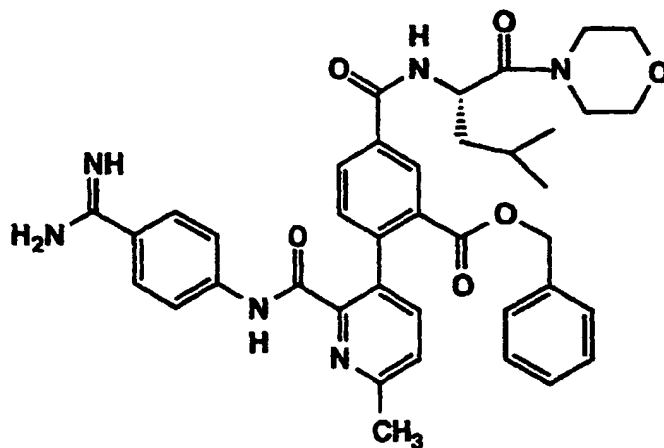
[0680]

40

45

50

55



EP 1 078 917 A1

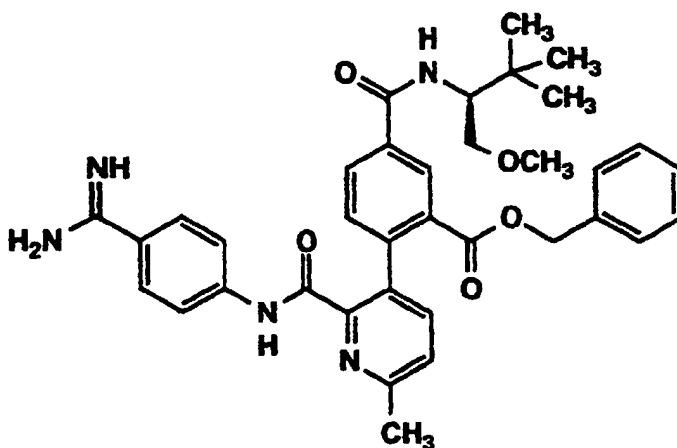
TLC : Rf 0.53 (Chloroform : Methanol : Acetic acid = 10 : 1 : 0.2) ;

NMR (200 MHz, CD₃OD) : δ 8.54 (d, J = 1.8 Hz, 1H), 8.07 (dd, J = 8.2, 1.8 Hz, 1H), 7.85 (d, J = 9.0 Hz, 2H), 7.76 (d, J = 9.0 Hz, 2H), 7.56 (d, J = 8.2 Hz, 1H), 7.43 (d, J = 8.2 Hz, 1H), 7.33 (d, J = 8.2 Hz, 1H), 7.25-7.15 (m, 3H), 7.20-7.10 (m, 2H), 5.13 (dd, J = 12.0, 4.8 Hz, 1H), 5.01 (like d, 2H), 3.9-3.6 (m, 6H), 3.60-3.40 (m, 2H), 2.64 (s, 3H), 1.90-1.70 (m, 2H), 1.70-1.50 (m, 1H), 1.01 (d, J = 6.2 Hz, 3H), 1.00 (d, J = 6.2 Hz, 3H).

Example 40(43)

Benzyl 2-[2-(4-amidinophenylcarbamoyl)-6-methyl-3-pyridyl]-5-(1(S)-methoxymethyl-2, 2-dimethylpropylcarbamoyl)benzoate

[0681]



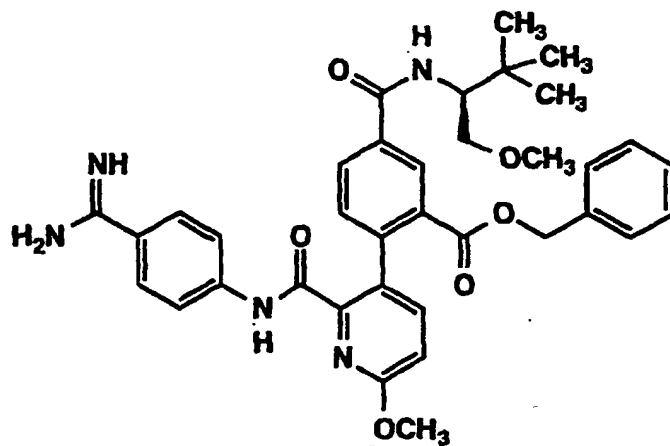
TLC : Rf 0.50 (Chloroform : Methanol : Water = 8 : 2 : 0.1) ;

NMR (200 MHz, CD₃OD) : δ 8.50 (d, J = 1.8 Hz, 1H), 8.03 (dd, J = 8.2, 1.8 Hz, 1H), 7.85 (d, J = 8.6 Hz, 2H), 7.76 (d, J = 8.6 Hz, 2H), 7.56 (d, J = 8.0 Hz, 1H), 7.43 (d, J = 8.0 Hz, 1H), 7.33 (d, J = 8.0 Hz, 1H), 7.26-7.16 (m, 3H), 7.09-7.04 (m, 2H), 5.01 (d, J = 3.2 Hz, 2H), 4.20 (dd, J = 9.2, 4.0 Hz, 1H), 3.72-3.50 (m, 2H), 3.34 (s, 3H), 2.64 (s, 3H), 1.02 (s, 9H).

Example 40(44)

Benzyl 2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-(1(S)-methoxymethyl-2, 2-dimethylpropylcarbamoyl)benzoate

[0682]



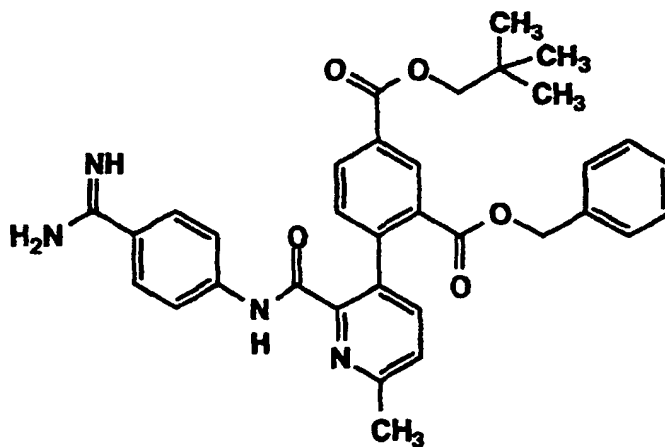
TLC : Rf 0.45 (Chloroform : Methanol : Water = 8 : 2 : 0.1) ;

NMR (200 MHz, CD₃OD) : δ 8.49 (d, J = 2.2 Hz, 1H), 8.01 (dd, J = 8.0, 2.2 Hz, 1H), 7.84 (d, J = 9.6 Hz, 2H), 7.76 (d, J = 9.6 Hz, 2H), 7.56 (d, J = 8.4 Hz, 1H), 7.32 (d, J = 8.2 Hz, 1H), 7.26-7.14 (m, 3H), 7.11-7.06 (m, 2H), 6.99 (d, J = 8.6 Hz, 1H), 5.03 (d, J = 8.8 Hz, 2H), 4.21 (dd, J = 8.8, 3.6 Hz, 1H), 3.68 (dd, J = 10.4, 4.2 Hz, 1H), 3.61-3.51 (m, 1H), 3.34 (s, 3H), 1.02 (s, 9H).

Example 40(45)

Benzyl 2-[2-(4-amidinophenylcarbamoyl)-6-methyl-3-pyridyl]-5-(2, 2-dimethylpropylcarbamoyl)benzoate

[0683]



EP 1 078 917 A1

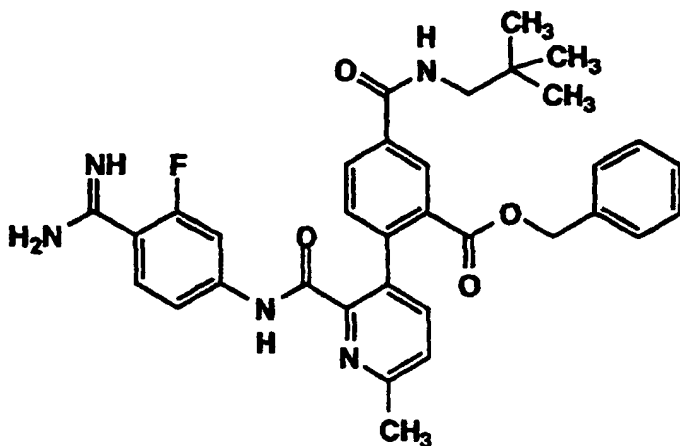
TLC : Rf 0.38 (Chloroform : Methanol : Water = 9 : 1 : 0.1) ;

NMR (200 MHz, CD₃OD) : δ 8.72 (d, J = 2.0 Hz, 1H), 8.23 (dd, J = 8.2, 2.0 Hz, 1H), 7.87 (dt, J = 9.2, 2.0 Hz, 2H), 7.78 (dt, J = 9.2, 2.0 Hz, 2H), 7.56 (d, J = 8.2 Hz, 1H), 7.44 (d, J = 8.2 Hz, 1H), 7.37 (d, J = 8.2 Hz, 1H), 7.26-7.16 (m, 3H), 7.10-7.06 (m, 2H), 4.98 (d, J = 11.2 Hz, 1H), 4.94 (d, J = 11.2 Hz, 1H), 4.08 (s, 2H), 2.66 (s, 3H), 1.07 (s, 9H).

Example 40(46)

Benzy 2-[2-(4-amidino-3-fluorophenylcarbamoyl)-6-methyl-3-pyridyl]-5-(2, 2-dimethylpropylcarbamoyl)benzoate

[0684]



TLC : Rf 0.37 (Chloroform : Methanol : Water = 8 : 2 : 0.1) ;

NMR (300 MHz, d₆-DMSO) : δ 9.22 (br s, 3H), 8.63 (t, J = 6.3 Hz, 1H), 8.40 (d, J = 1.8 Hz, 1H), 8.09 (dd, J = 7.8, 1.8 Hz, 1H), 7.82 (dd, J = 13.5, 1.8 Hz, 1H), 7.72-7.60 (m, 3H), 7.52 (d, J = 8.1 Hz, 1H), 7.36 (d, J = 8.1 Hz, 1H), 7.28-7.20 (m, 3H), 7.12-7.08 (m, 2H), 5.03 (s, 2H), 3.13 (d, J = 6.3 Hz, 2H), 2.64 (s, 3H), 0.91 (s, 9H).

Example 40(47)

Dibenzyl 4-[2-(4-amidinophenylcarbamoyl)-6-methyl-3-pyridyl]isophthalate

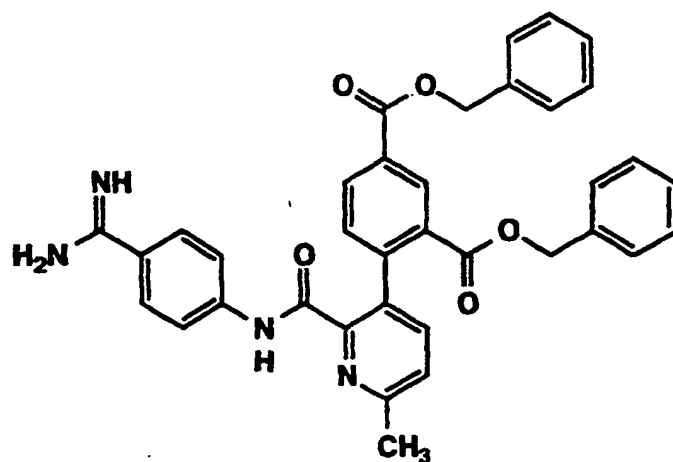
5 [0685]

10

15

20

25



30

TLC : Rf 0.50 (Chloroform : Methanol : Water = 10 : 2 : 0.5) ;

NMR (200 MHz, CD₃OD) : δ 8.67 (d, J = 1.8 Hz, 1H), 8.18 (dd, J = 7.6, 1.8 Hz, 1H), 7.83-7.72 (m, 4H), 7.50-7.29 (m, 9H), 7.20-7.17 (m, 2H), 7.04-6.98 (m, 2H), 5.38 (s, 2H), 4.97 (d, J = 4.0 Hz, 2H), 2.62 (s, 3H).

Example 40(48)

Benzyl 2'-(4-amidinophenylcarbamoyl)-5'-benzyloxycarbonylamino-4-(2, 2-dimethylpropylcarbamoyl)-2-biphenylcarboxylate

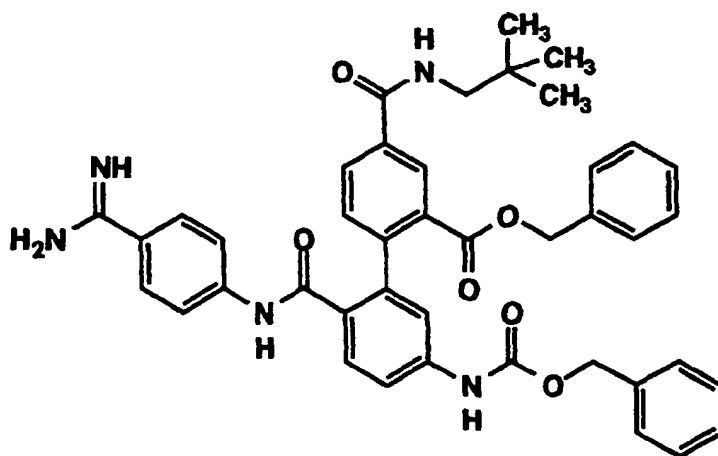
35 [0686]

40

45

50

55



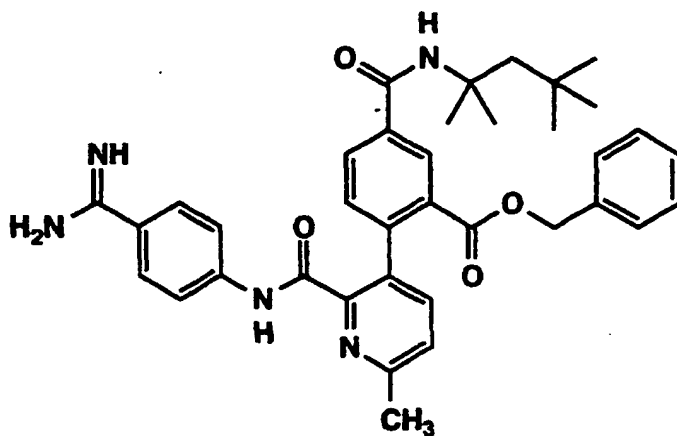
TLC : Rf 0.29 (Chloroform : Methanol : Water = 8 : 2 : 0.2) ;

NMR (200 MHz, CD₃OD) : δ 8.32 (d, J = 2.0 Hz, 1H), 7.96 (dd, J = 8.0, 2.0 Hz, 1H), 7.70-7.58 (m, 6H), 7.46-7.35 (m, 6H), 7.23-7.10 (m, 6H), 5.21 (s, 2H), 5.13 (s, 2H), 3.21 (s, 2H), 0.96 (s, 9H).

Example 40(49)

Benzyl 2-[2-(4-amidinophenylcarbamoyl)-6-methyl-3-pyridyl]-5-(1, 1, 3, 3-tetramethylbutylcarbamoyl)benzoate

[0687]



TLC : Rf 0.64 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (300 MHz, CD₃OD) : δ 8.40 (d, J = 1.8 Hz, 1H), 7.92 (dd, J = 8.0, 1.8 Hz, 1H), 7.84 (d, J = 9.0 Hz, 2H), 7.76 (d, J = 9.0 Hz, 2H), 7.54 (d, J = 8.0 Hz, 1H), 7.43 (d, J = 8.0 Hz, 1H), 7.29 (d, J = 8.0 Hz, 1H), 7.25-7.16 (m, 3H), 7.10-7.04 (m, 2H), 5.04 (brd, J = 12 Hz, 1H), 4.97 (brd, J = 12 Hz, 1H), 2.64 (s, 3H), 2.00 (s, 2H), 1.51 (s, 6H), 1.05 (s, 9H).

Example 40(50)

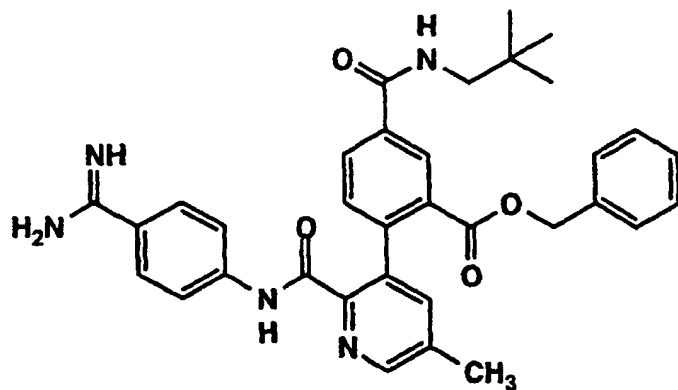
Benzyl 2-[2-(4-amidinophenylcarbamoyl)-5-methyl-3-pyridyl]-5-(2, 2-dimethyl propylcarbamoyl)benzoate

5 [0688]

10

15

20



25

TLC : Rf 0.29 (Chloroform : Methanol : Water = 8 : 2 : 0.2) ;
 NMR (200 MHz, CD₃OD) : δ 8.54 (d, J = 2.0 Hz, 1H), 8.44 (d, J = 2.0 Hz, 1H), 8.05 (dd, J = 8.0, 2.0 Hz, 1H), 7.85 (d, J = 9.0 Hz, 2H), 7.75 (d, J = 9.0 Hz, 2H), 7.49 (d, J = 2.0 Hz, 1H), 7.34 (d, J = 8.0 Hz, 1H), 7.24-7.18 (m, 3H), 7.11-7.06 (m, 2H), 5.03 (s, 2H), 3.27 (s, 2H), 2.41 (s, 3H), 1.00 (s, 9H).

30 Example 40(51)

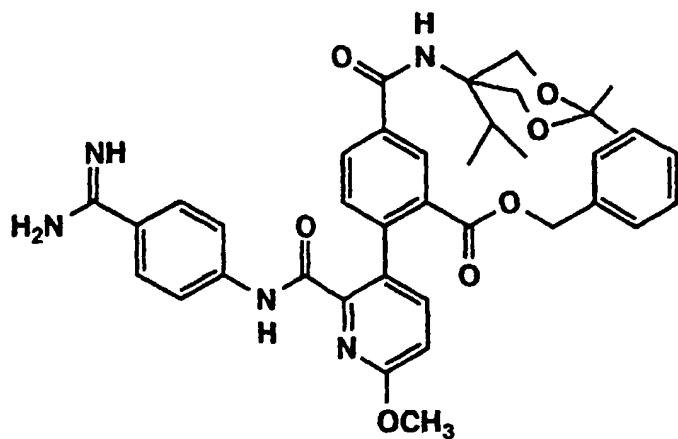
Benzyl 2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-[[5-(1-methylethyl)-2, 2-dimethyldioxan-5-yl]carbamoyl]benzoate

35 [0689]

40

45

50



55

TLC : Rf 0.75 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;
 NMR (300 MHz, CD₃OD) : δ 8.47 (d, J = 1.8 Hz, 1H), 7.98 (dd, J = 7.8, 1.8 Hz, 1H), 7.85-7.75 (m, 4H), 7.55 (d, J

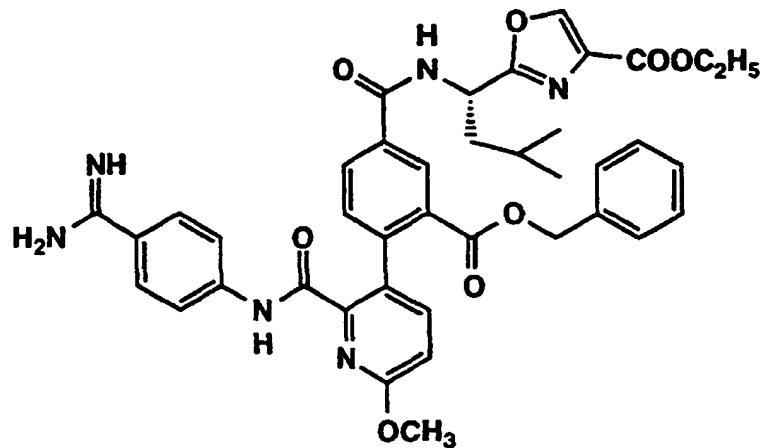
EP 1 078 917 A1

= 8.1 Hz, 1H), 7.31 (d, J = 8.1 Hz, 1H), 7.23-7.20 (m, 3H), 7.07 (d, J = 7.5 Hz, 1H), 7.07 (d, J = 8.4 Hz, 1H), 7.00 (d, J = 8.7 Hz, 1H), 5.02 (d, J = 13.4 Hz, 2H), 4.23 (d, J = 12.0 Hz, 2H), 4.07 (d, J = 12.0 Hz, 2H), 4.06 (s, 3H), 2.50 (m, 1H), 1.44 (s, 3H), 1.37 (s, 3H), 1.02 (d, J = 7.2 Hz, 6H).

5 Example 40(52)

Benzyl 2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-[1(S)-(4-ethoxycarbonyloxazol-2-yl)-3-methylbutyl]carbamoyl]benzoate

10 [0690]



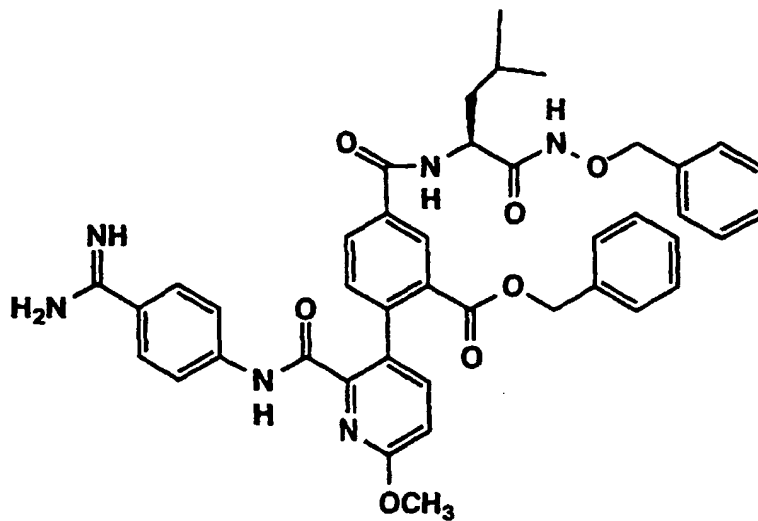
TLC : Rf 0.86 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (300 MHz, CD₃OD) : δ 8.55 (d, J = 2.0 Hz, 1H), 8.50 (s, 1H), 8.07 (dd, J = 8.0, 2.0 Hz, 1H), 7.83 (d, J = 9.0 Hz, 2H), 7.77 (d, J = 9.0 Hz, 2H), 7.55 (d, J = 8.4 Hz, 1H), 7.33 (d, J = 8.0 Hz, 1H), 7.26-7.16 (m, 3H), 7.10-7.05 (m, 2H), 6.99 (d, J = 8.4 Hz, 1H), 5.45 (dd, J = 9.6, 6.3 Hz, 1H), 5.02 (brd, J = 12 Hz, 1H), 4.97 (brd, J = 12 Hz, 1H), 4.34 (q, J = 7.2 Hz, 2H), 4.06 (s, 3H), 2.07-1.87 (m, 2H), 1.83-1.68 (m, 1H), 1.35 (t, J = 7.2 Hz, 3H), 1.03 (d, J = 6.6 Hz, 3H), 1.01 (d, J = 6.3 Hz, 3H).

Example 40(53)

Benzyl 2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-[(1(S)-N-benzyloxycarbamoyl)-3-methylbutylcarbamoyl]benzoate

[0691]



TLC : Rf 0.58 (Chloroform : Methanol : Water = 8 : 2 : 0.2) ;

NMR (300 MHz, DMSO- d_6) : δ 10.55 (s, 1H), 9.10 (br, 3H), 8.81 (d, J = 7.2 Hz, 1H), 8.45 (dd, J = 8.1, 1.5 Hz, 1H), 7.90 (d, J = 9.0 Hz, 2H), 7.81 (d, J = 9.0 Hz, 2H), 7.66 (d, J = 8.4 Hz, 1H), 7.39-7.34 (m, 5H), 7.27-7.19 (m, 3H), 7.12-7.06 (m, 3H), 5.05 (s, 2H), 4.80 (s, 2H), 4.43 (m, 1H), 4.08 (s, 3H), 1.80-1.60 (m, 2H), 1.49 (m, 1H), 0.90 (d, J = 6.3 Hz, 3H), 0.87 (d, J = 6.6 Hz, 3H).

Example 40(54)

Benzyl 2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-(2, 2-dimethyl propylcarbamoyl)-4-methylbenzoate

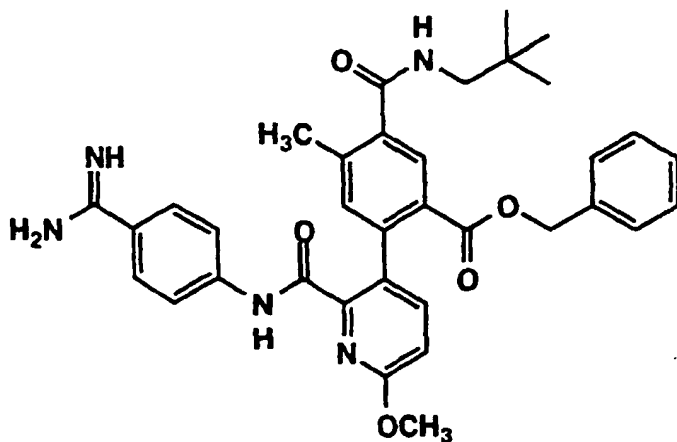
5 [0692]

10

15

20

25



TLC : Rf 0.47 (Chloroform : Methanol : Water = 8 : 2 : 0.2) ;
 NMR (200 MHz, CD₃OD) : δ 8.05 (s, 1H), 7.84 (d, J = 9.0 Hz, 2H), 7.77 (d, J = 9.0 Hz, 2H), 7.52 (d, J = 8.4 Hz, 1H),
 30 7.26-7.17 (m, 3H), 7.12 (s, 1H), 7.09-7.04 (m, 2H), 6.98 (d, J = 8.4 Hz, 1H), 5.04 (d, J = 12.0 Hz, 1H), 4.95 (d, J =
 12.0 Hz, 1H), 4.06 (s, 3H), 3.23 (s, 2H), 2.46 (s, 3H), 1.01 (s, 9H).

Example 40(55)

35 Dibenzyl 4-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]isophthalate

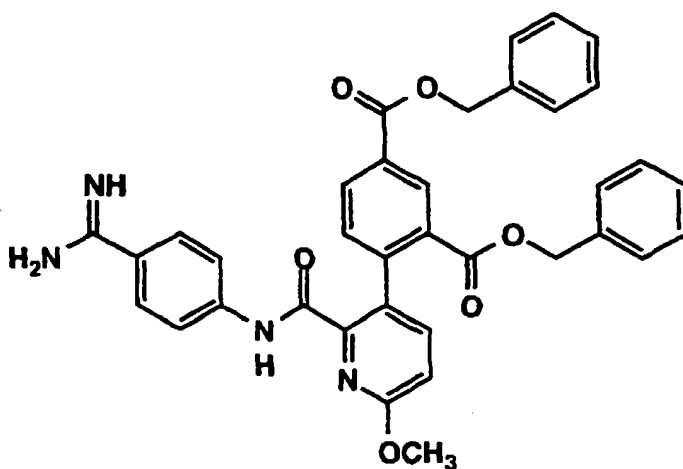
[0693]

40

45

50

55



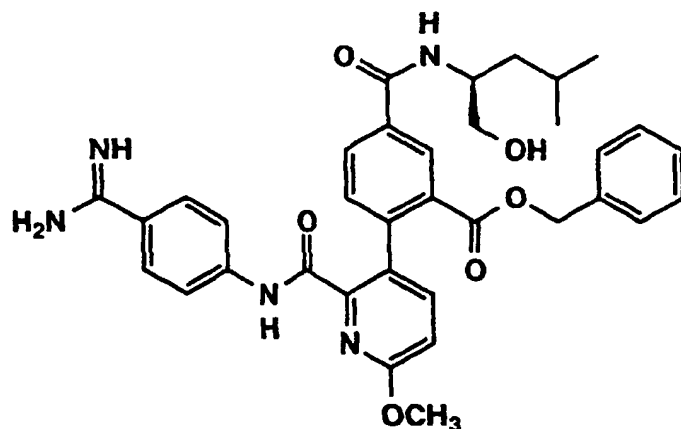
TLC : Rf 0.17 (Chloroform : Methanol : Water = 9 : 1 : 0.1) ;

NMR (200 MHz, CD₃OD) : δ 8.07 (d, J = 1.8 Hz, 1H), 8.23 (dd, J = 8.0, 1.8 Hz, 1H), 7.84 (d, J = 9.4 Hz, 2H), 7.77 (d, J = 9.4 Hz, 2H), 7.54 (d, J = 8.4 Hz, 1H), 7.50-7.32 (m, 5H), 7.26-7.14 (m, 3H), 7.09-7.04 (m, 2H), 6.99 (d, J = 8.4 Hz, 1H), 5.42 (s, 2H), 5.05 (m, 1H), 5.00 (m, 1H), 4.07 (s, 3H).

Example 40(56)

Benzyl 2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-(1(S)-hydroxymethyl-3-methylbutylcarbamoyl)-4-methylbenzoate

[0694]



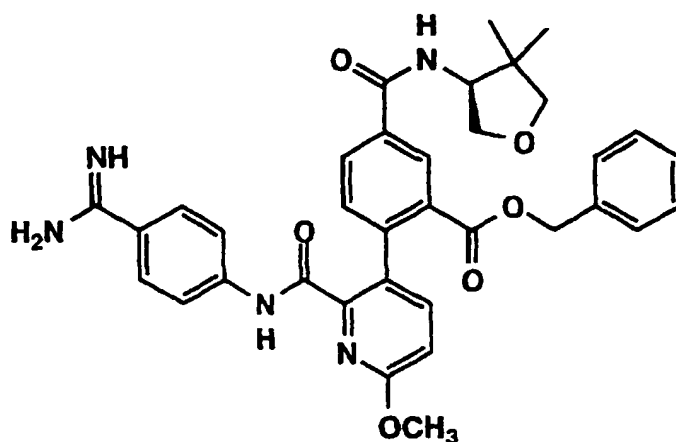
TLC : Rf 0.58 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (300 MHz, CD₃OD) : δ 8.51 (d, J = 1.8 Hz, 1H), 8.03 (dd, J = 8.0, 1.8 Hz, 1H), 7.83 (d, J = 9.0 Hz, 2H), 7.77 (d, J = 9.0 Hz, 2H), 7.55 (d, J = 8.4 Hz, 1H), 7.31 (d, J = 8.0 Hz, 1H), 7.25-7.16 (m, 3H), 7.12-7.05 (m, 2H), 6.99 (d, J = 8.4 Hz, 1H), 5.07 (brd, J = 12 Hz, 1H), 4.98 (brd, J = 12 Hz, 1H), 4.32-4.22 (m, 1H), 4.06 (s, 3H), 3.61 (d, J = 5.7 Hz, 2H), 1.80-1.65 (m, 1H), 1.65-1.40 (m, 2H), 0.98 (d, J = 6.6 Hz, 6H).

Example 40(57)

Benzyl 2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-[(4, 4-dimethyloxolan-3(S)-yl)carbamoyl]-4-methylbenzoate

[0695]



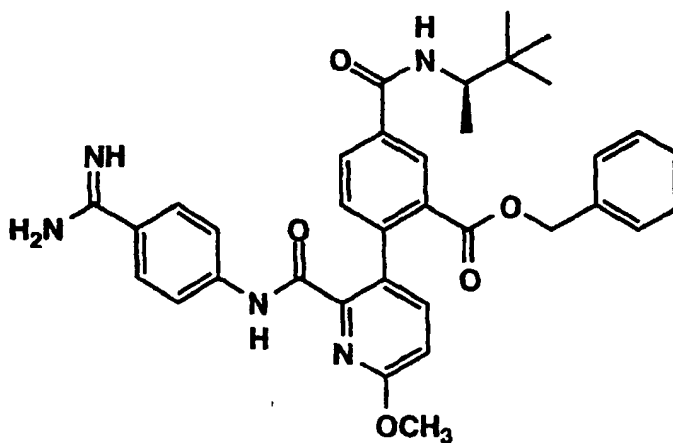
TLC : Rf 0.70 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (300 MHz, CD₃OD) : δ 8.50 (d, J = 1.8 Hz, 1H), 8.02 (dd, J = 8.0, 1.8 Hz, 1H), 7.83 (d, J = 9.0 Hz, 2H), 7.77 (d, J = 9.0 Hz, 2H), 7.55 (d, J = 8.4 Hz, 1H), 7.33 (d, J = 8.0 Hz, 1H), 7.24-7.17 (m, 3H), 7.12-7.05 (m, 2H), 6.99 (d, J = 8.4 Hz, 1H), 5.07 (brd, J = 12 Hz, 1H), 4.98 (brd, J = 12 Hz, 1H), 4.48 (dd, J = 7.5, 5.4 Hz, 1H), 4.23 (dd, J = 9.3, 7.5 Hz, 1H), 4.06 (s, 3H), 3.77 (dd, J = 9.3, 5.4 Hz, 1H), 3.64 (d, J = 8.4 Hz, 1H), 3.59 (d, J = 8.4 Hz, 1H), 1.21 (s, 3H), 1.08 (s, 3H).

Example 40(58)

Benzyl 2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-(1(R), 2, 2-trimethylpropylcarbamoyl)benzoate

[0696]



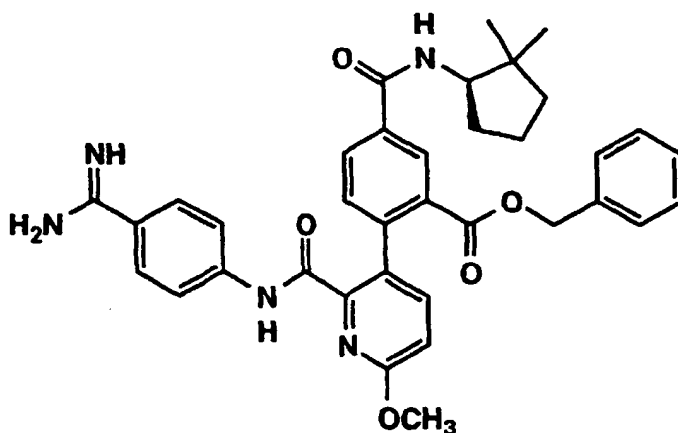
TLC : Rf 0.65 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (300 MHz, CD₃OD) : δ 8.46 (d, J = 1.8 Hz, 1H), 7.99 (dd, J = 8.0, 1.8 Hz, 1H), 7.83 (d, J = 9.0 Hz, 2H), 7.77 (d, J = 9.0 Hz, 2H), 7.55 (d, J = 8.4 Hz, 1H), 7.31 (d, J = 8.0 Hz, 1H), 7.25-7.16 (m, 3H), 7.10-7.06 (m, 2H), 6.99 (d, J = 8.4 Hz, 1H), 5.07 (brd, J = 12 Hz, 1H), 4.98 (brd, J = 12 Hz, 1H), 4.10 (q, J = 7.0 Hz, 1H), 4.06 (s, 3H), 1.20 (d, J = 7.0 Hz, 3H), 1.00 (s, 9H).

Example 40(59)

Benzyl 2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-[(1(R)-2, 2-dimethylcyclopentyl)carbamoyl]benzoate

[0697]



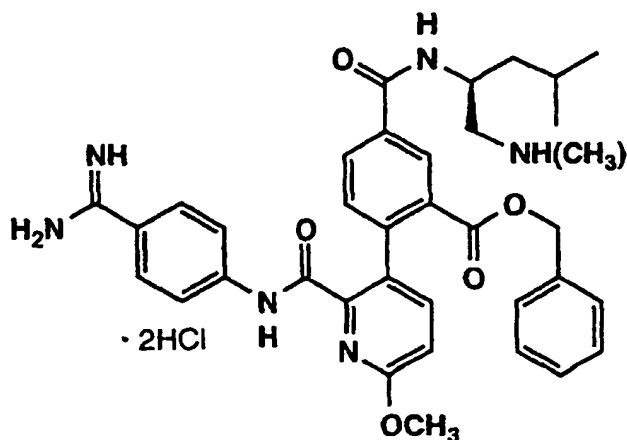
TLC : Rf 0.70 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (300 MHz, CD₃OD) : δ 8.48 (d, J = 1.8 Hz, 1H), 8.00 (dd, J = 8.0, 1.8 Hz, 1H), 7.83 (d, J = 9.0 Hz, 2H), 7.77 (d, J = 9.0 Hz, 2H), 7.54 (d, J = 8.4 Hz, 1H), 7.31 (d, J = 8.0 Hz, 1H), 7.26-7.16 (m, 3H), 7.10-7.05 (m, 2H), 6.98 (d, J = 8.4 Hz, 1H), 5.07 (brd, J = 12 Hz, 1H), 4.98 (brd, J = 12 Hz, 1H), 4.21 (brt, J = 7.0 Hz, 1H), 4.06 (s, 3H), 2.15-2.03 (m, 1H), 1.84-1.54 (m, 5H), 1.09 (s, 3H), 0.98 (s, 3H).

Example 40(60)

Benzyl 2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-[(1(S)-methylaminomethyl-3-methylbutyl)carbamoyl]benzoate dihydrochloride

[0698]



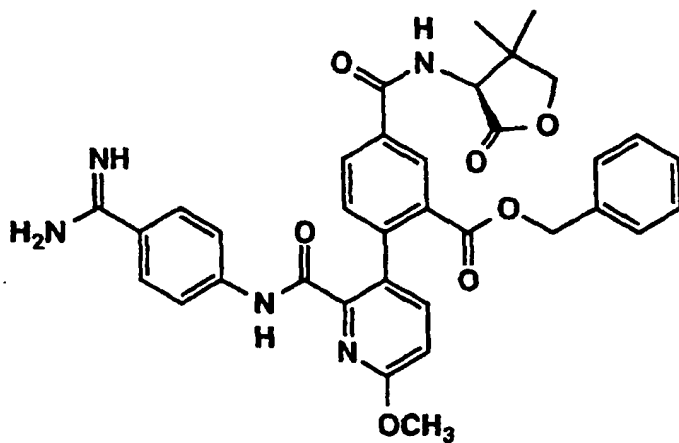
TLC : Rf 0.38 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (300 MHz, CD₃OD) : δ 8.60 (d, J = 1.8 Hz, 1H), 8.12 (dd, J = 8.2, 1.8 Hz, 1H), 7.78 (d, J = 9.1 Hz, 2H), 7.55 (d, J = 8.4 Hz, 1H), 7.36 (d, J = 8.2 Hz, 1H), 7.24-7.18 (m, 3H), 7.10-7.05 (m, 2H), 7.01 (d, J = 8.4 Hz, 1H), 5.04 (d, J = 8.2 Hz, 2H), 4.54 (m, 1H), 4.07 (s, 3H), 2.76 (s, 3H), 1.80-1.64 (m, 2H), 1.40 (m, 1H), 1.01 (d, J = 6.3 Hz, 3H), 0.99 (d, J = 6.6 Hz, 3H).

Example 40(61)

Benzyl 2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-[(4, 4-dimethyl-2-oxoxolan-3(S)-yl)carbamoyl]benzoate

[0699]



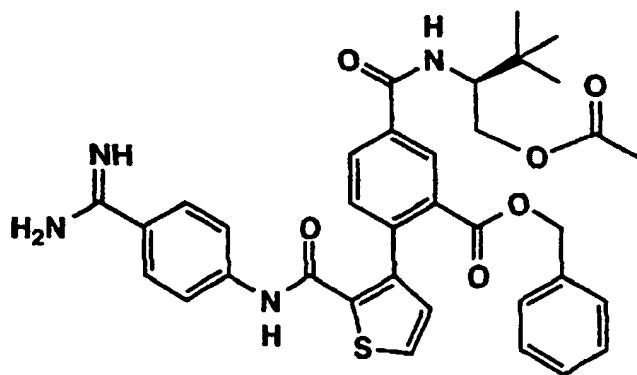
TLC : Rf 0.70 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (300 MHz, CD₃OD) : δ 8.57 (d, J = 1.8 Hz, 1H), 8.09 (dd, J = 8.0, 1.8 Hz, 1H), 7.83 (d, J = 9.0 Hz, 2H), 7.77 (d, J = 9.0 Hz, 2H), 7.56 (d, J = 8.4 Hz, 1H), 7.35 (d, J = 8.0 Hz, 1H), 7.28-7.17 (m, 3H), 7.10-7.04 (m, 2H), 6.99 (d, J = 8.4 Hz, 1H), 5.07 (brd, J = 12 Hz, 1H), 5.00 (s, 1H), 4.99 (brd, J = 12 Hz, 1H), 4.19 (d, J = 9.0 Hz, 1H), 4.14 (d, J = 9.0 Hz, 1H), 1.27 (s, 3H), 1.12 (s, 3H).

Example 40(62)

Benzyl 2-[2-(4-amidinophenylcarbamoyl)-3-thienyl]-5-[(1(S)-acetyloxymethyl-2,2-dimethylpropyl)carbamoyl]benzoate

[0700]



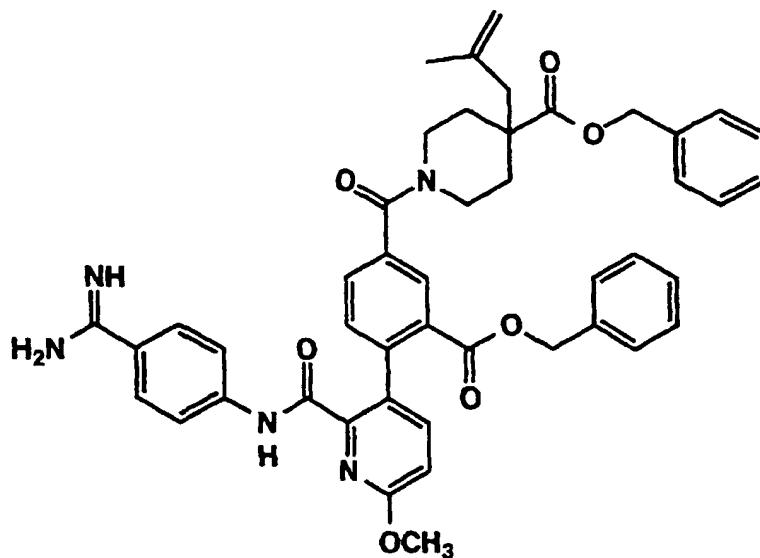
TLC : Rf 0.30 (Chloroform : Methanol : Acetic acid = 10 : 1 : 0.2) ;

NMR (200 MHz, CD₃OD) : δ 8.33 (d, J = 2.0 Hz, 1H), 7.99 (dd, J = 8.0, 2.0 Hz, 1H), 7.71 (d, J = 9.2 Hz, 2H), 7.70-7.60 (m, 1H), 7.62 (d, J = 9.2 Hz, 2H), 7.49 (d, J = 8.0 Hz, 1H), 7.30-7.15 (m, 5H), 7.06 (d, J = 5.2 Hz, 1H), 5.13 (s, 2H), 4.46 (dd, J = 10.4, 3.0 Hz, 1H), 4.26 (dd, J = 10.4, 3.0 Hz, 1H), 4.13 (t, J = 10.4 Hz, 1H), 1.95 (s, 3H), 1.03 (s, 9H).

Example 40(63)

Benzyl 2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-[[4-benzoyloxy carbonyl-4-(2-methyl-2-propenyl)pipe-
ridinyl]carbonyl]benzoate

[0701]



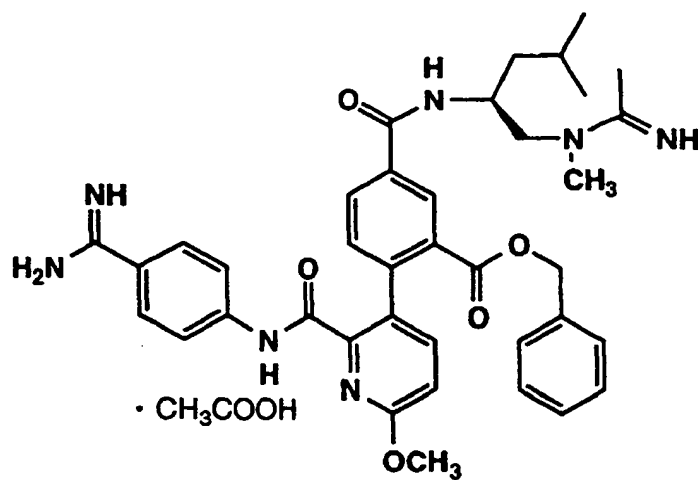
TLC : Rf 0.58 (Chloroform : Methanol : Water = 8 : 2 : 0.1) ;

NMR (300 MHz, CD₃OD) : δ 8.05 (d, J = 2.1 Hz, 1H), 7.83 (d, J = 9.0 Hz, 2H), 7.77 (d, J = 9.0 Hz, 2H), 7.61 (dd, J = 8.1, 2.1 Hz, 1H), 7.55 (d, J = 8.4 Hz, 1H), 7.44-7.29 (m, 5H), 7.31 (d, J = 7.8 Hz, 1H), 7.26-7.16 (m, 3H), 7.09-7.05 (m, 2H), 6.99 (d, J = 8.7 Hz, 1H), 5.18 (s, 2H), 5.01 (d, J = 17.1 Hz, 2H), 4.80 (m, 1H), 4.67 (s, 1H), 4.45-4.30 (m, 2H*1/2, each of rotamers), 4.06 (s, 3H), 3.80-3.70 (m, 2H*1/2, each of rotamers), 3.31-3.20 (m, 2H*1/2, each of rotamers), 3.10-3.00 (m, 2H*1/2, each of rotamers), 2.40 (m, 2H), 2.40-2.20 (m, 2H*1/2, each of rotamers), 2.20-2.10 (m, 2H*1/2, each of rotamers), 1.62 (s, 3H), 1.62-1.50 (m, 2H).

Example 40(64)

Benzyl 2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-[1(S)-[N-methyl-N-(1-iminoethyl)aminomethyl]-3-methylbutyl]benzoate acetic acetate

[0702]



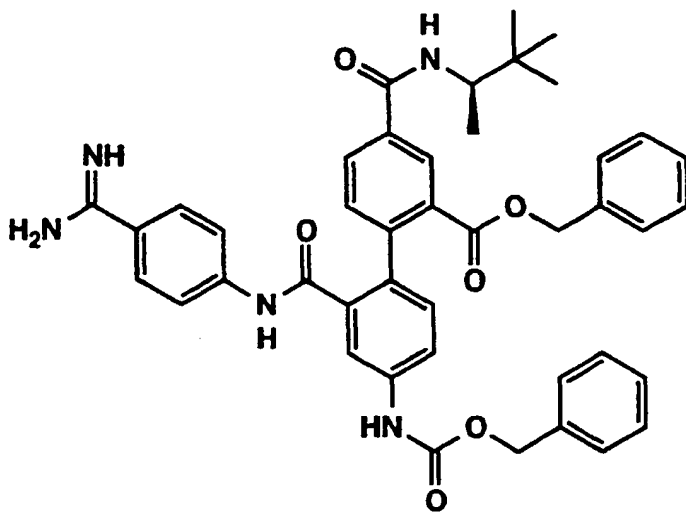
TLC : Rf 0.25 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (300 MHz, CD₃OD) : δ 8.52 and 8.49 (s, 1H), 8.04 (m, 1H), 7.84 (d, J = 9.0 Hz, 2H), 7.79 (d, J = 9.0 Hz, 2H), 7.53 (d, J = 8.4 Hz, 1H), 7.26-7.06 (m, 5H), 7.00 (d, J = 8.4 Hz, 1H), 5.08 (d, J = 12.6 Hz, 1H), 4.97 (d, J = 12.6 Hz, 1H), 4.50 (m, 1H), 4.07 (s, 3H), 3.64 (d, J = 6.9 Hz, 2H), 3.21 (s, 3H), 2.35 and 2.32 (s, 3H), 1.99 (s, 3H), 1.90-1.62 (m, 2H), 1.41 (m, 1H), 0.99 (m, 6H).

Example 40(65)

Benzyl 2'-(4-amidinophenylcarbamoyl)-4'-benzyloxycarbonylamino-4-(1(R), 2, 2-trimethylpropylcarbamoyl)-2-biphenyl-carboxylate

[0703]



TLC : Rf 0.46 (Chloroform : Methanol : Water = 8 : 2 : 0.2) ;

NMR (200 MHz, CDCl₃) : δ 8.25 (d, J = 2.0 Hz, 1H), 8.15 (br.d, J = 9.6 Hz, 1H), 7.90 (dd, J = 8.0, 2.0 Hz, 1H), 7.81 (d, J = 2.0 Hz, 1H), 7.67 (d, J = 9.0 Hz, 2H), 7.60 (d, J = 9.0 Hz, 2H), 7.51-7.31 (m, 7H), 7.22-7.08 (m, 6H), 5.23 (s, 2H), 5.10 (s, 2H), 4.05 (m, 1H), 1.15 (d, J = 7.0 Hz, 3H), 0.94 (s, 9H).

Example 40(66)

Benzyl 2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-[1-(2, 2-dimethylpropyl)tetrazol-5-yl]benzoate

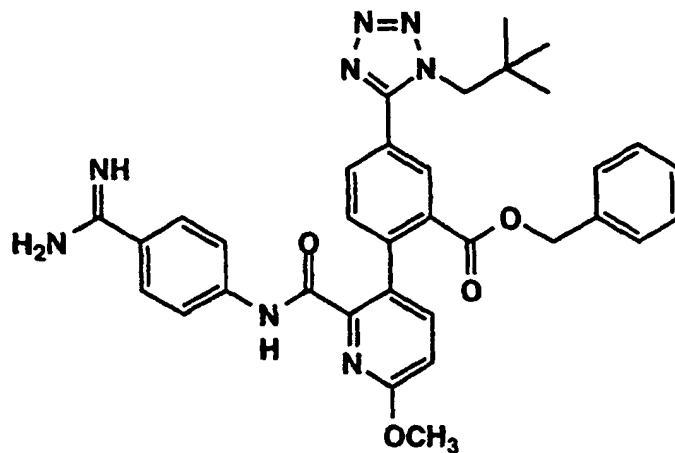
5 [0704]

10

15

20

25



30

35

40

45

50

55

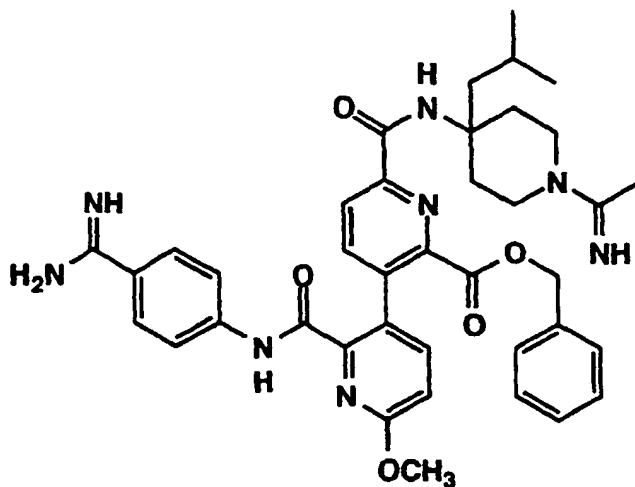
TLC : Rf 0.48 (Chloroform : Methanol : Acetic acid = 10 : 1 : 0.2) ;

NMR (300 MHz, CD₃OD) : δ 8.38 (d, J = 2.0 Hz, 1H), 7.95 (dd, J = 8.0, 2.0 Hz, 1H), 7.85 (d, J = 9.0 Hz, 2H), 7.78 (d, J = 9.0 Hz, 2H), 7.62 (d, J = 8.4 Hz, 1H), 7.48 (d, J = 8.0 Hz, 1H), 7.3-7.1 (m, 3H), 7.15-7.05 (m, 2H), 7.01 (d, J = 8.4 Hz, 1H), 5.09 (d, J = 11.7 Hz, 1H), 4.99 (d, J = 11.7 Hz, 1H), 4.44 (s, 2H), 4.07 (s, 3H), 0.90 (s, 9H).

Example 40(67)

Benzyl 2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-[[1-(1-iminoethyl)-4-(2-methylpropyl)piperidin-4-yl]carbamoyl]benzoate

[0705]



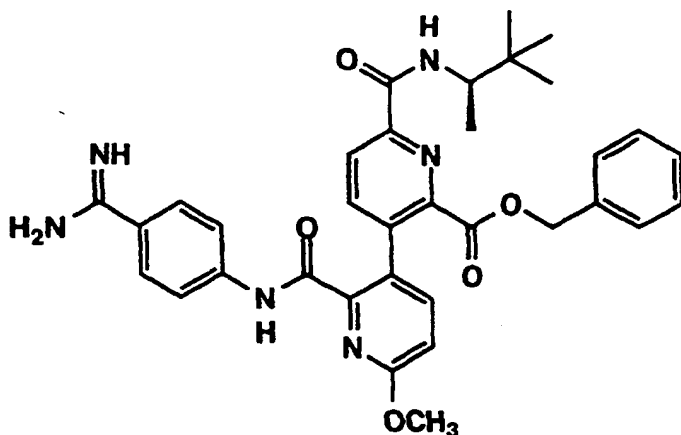
TLC : Rf 0.87 (Ethyl acetate : Acetic acid : Water = 3 : 1 : 1) ;

NMR (300 MHz, CD₃OD) : δ 8.46 (d, J = 1.8 Hz, 1H), 8.01 (dd, J = 8.1, 1.8 Hz, 1H), 7.83 (d, J = 9.3 Hz, 2H), 7.78 (d, J = 9.3 Hz, 2H), 7.53 (d, J = 8.7 Hz, 1H), 7.33 (d, J = 8.1 Hz, 1H), 7.25-7.17 (m, 3H), 7.08-7.05 (m, 2H), 6.99 (d, J = 8.7 Hz, 1H), 5.02 (d, J = 18.6 Hz, 2H), 4.06 (s, 3H), 3.96-3.84 (m, 2H), 3.59-3.37 (m, 2H), 2.73-2.62 (m, 2H), 2.34 (s, 3H), 1.86-1.73 (m, 5H), 0.98 (d, J = 6.0 Hz, 6H).

Example 40(68)

Benzyl 3-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-6-[(1(R), 2, 2-trimethylpropyl)carbamoyl]-2-pyridinecarboxylate

[0706]



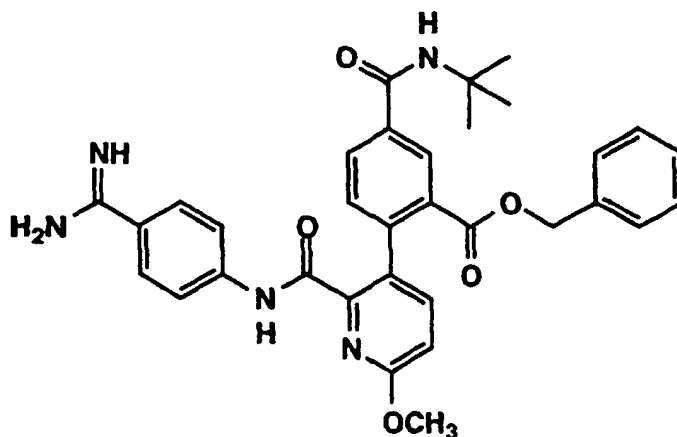
TLC : Rf 0.30 (Chloroform : Methanol : Water = 8 : 2 : 0.2) ;

NMR (200 MHz, CD₃OD) : δ 8.29 (d, J = 8.0 Hz, 1H), 7.87 (d, J = 8.0 Hz, 1H), 7.85 (d, J = 9.0 Hz, 2H), 7.77 (d, J = 9.0 Hz, 2H), 7.61 (d, J = 8.4 Hz, 1H), 7.28-7.17 (m, 3H), 7.09-7.04 (m, 2H), 7.02 (d, J = 8.4 Hz, 1H), 5.20-4.94 (m, 2H), 4.07 (s, 3H), 4.06 (m, 1H), 1.24 (d, J = 7.0 Hz, 3H), 1.00 (s, 9H).

Example 40(69)

Benzyl 2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-(t-butyl carbamoyl)benzoate

[0707]



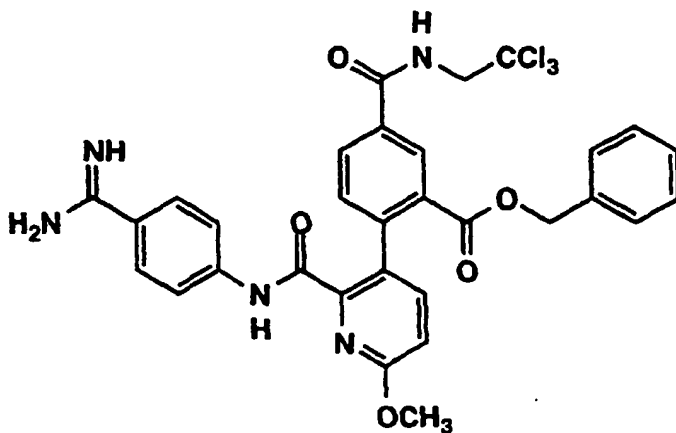
TLC : Rf 0.40 (Chloroform : Methanol : Acetic acid = 10 : 1 : 0.5) ;

NMR (200 MHz, CD₃OD) : d 8.41 (d, J = 1.8 Hz, 1H), 7.93 (dd, J = 8.4, 1.8 Hz, 1H), 7.83 (d, J = 9.0 Hz, 2H), 7.82 (d, J = 9.0 Hz, 2H), 7.53 (d, J = 8.4 Hz, 1H), 7.27 (d, J = 8.4 Hz, 1H), 7.20-7.04 (m, 5H), 6.97 (d, J = 8.4 Hz, 1H), 5.01 (d, J = 8.2 Hz, 2H), 4.06 (s, 3H), 1.48 (s, 9H).

Example 40(70)

Benzy 2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-(2, 2, 2-trichloroethylcarbamoyl)benzoate

[0708]



TLC : Rf 0.25 (Chloroform : Methanol : Acetic acid = 10 : 1 : 0.5) ;

NMR (300 MHz, CD₃OD) : d 8.57 (d, J = 1.8 Hz, 1H), 8.08 (dd, J = 7.8, 1.8 Hz, 1H), 7.83 (d, J = 9.0 Hz, 2H), 7.77 (d, J = 9.0 Hz, 2H), 7.56 (d, J = 8.4 Hz, 1H), 7.36 (d, J = 7.8 Hz, 1H), 7.25-7.07 (m, 6H), 7.00 (d, J = 8.4 Hz, 1H), 5.03 (d, J = 17.7 Hz, 2H), 4.49 (s, 2H), 4.07 (s, 3H).

Example 40(71)

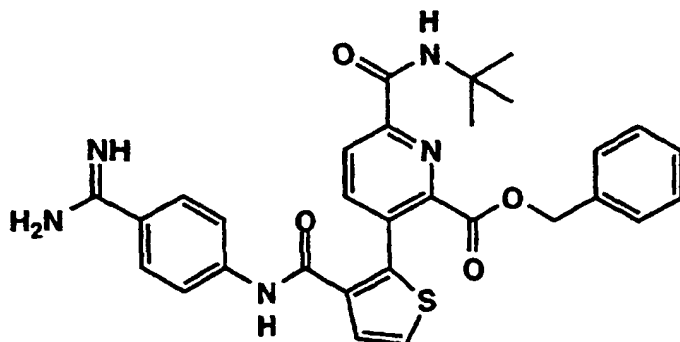
Benzyl 2-[3-(4-amidinophenylcarbamoyl)-2-thienyl]-6-(t-butylcarbamoyl)-2-pyridinecarboxylate

5 [0709]

10

15

20



25

TLC : Rf 0.30 (Chloroform : Methanol : Water = 8 : 2 : 0.2) ;

NMR (300 MHz, CD₃OD) : δ 8.23 (d, J = 8.0 Hz, 1H), 8.04 (d, J = 8.0 Hz, 1H), 7.79 (d, J = 9.0 Hz, 2H), 7.74 (d, J = 9.0 Hz, 2H), 7.59 (d, J = 5.4 Hz, 1H), 7.52 (d, J = 5.4 Hz, 1H), 7.25-7.21 (m, 3H), 7.16-7.13 (m, 2H), 5.13 (s, 2H), 1.48 (s, 9H).

Example 40(72)

30 Benzyl 2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-(2, 2, 2-trifluoroethylcarbamoyl)benzoate

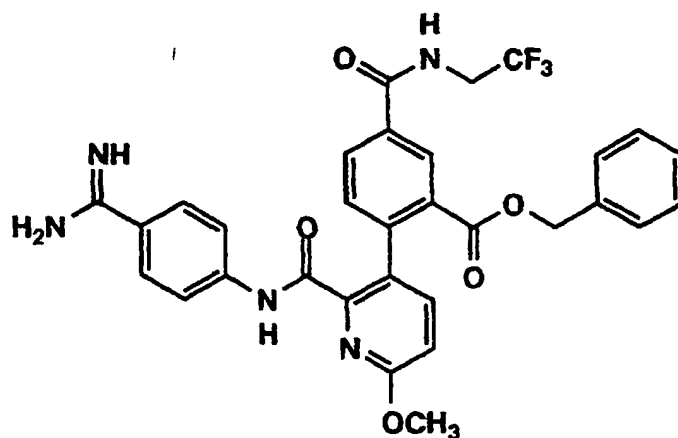
[0710]

35

40

45

50



55

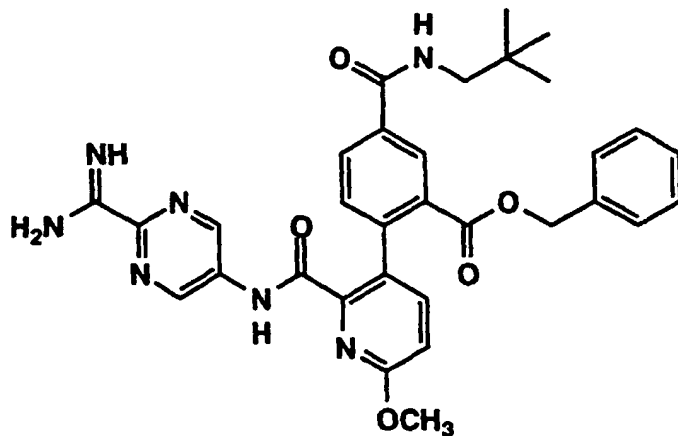
TLC : Rf 0.41 (Chloroform : Methanol : Water = 8 : 2 : 0.2) ;

NMR (300 MHz, CD₃OD) : δ 8.56 (d, J = 1.8 Hz, 1H), 8.06 (dd, J = 8.1, 1.8 Hz, 1H), 7.83 (d, J = 9.0 Hz, 2H), 7.78 (d, J = 9.0 Hz, 2H), 7.54 (d, J = 8.7 Hz, 1H), 7.35 (d, J = 8.1 Hz, 1H), 7.25-7.17 (m, 3H), 7.07 (d, J = 8.7 Hz, 1H), 6.99 (d, J = 8.7 Hz, 1H), 5.07 (d, J = 11.7 Hz, 1H), 4.99 (d, J = 11.7 Hz, 1H), 4.13 (q, J = 9.3 Hz, 2H), 4.07 (s, 3H).

Example 40(73)

Benzyl 2-[2-[(2-amidinopyrimidin-5-yl)carbamoyl]-6-methoxy-3-pyridyl]-5-(2, 2-dimethylpropylcarbamoyl)benzoate

[0711]



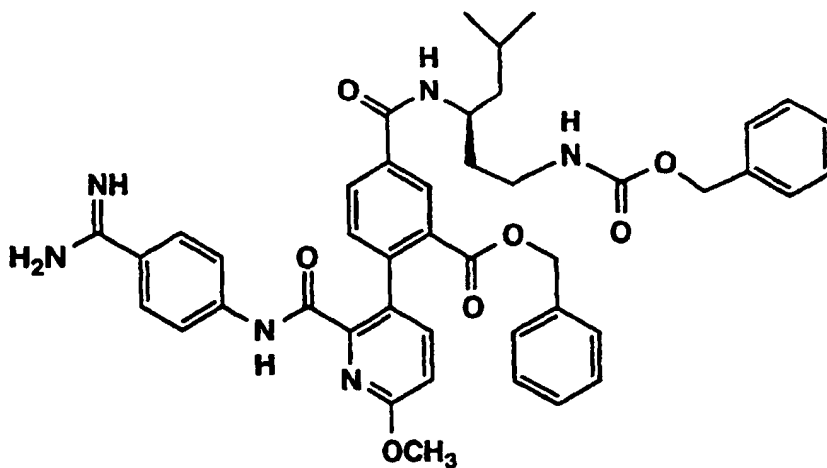
TLC : Rf 0.57 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (300 MHz, d₆-DMSO) : δ 11.05-10.85 (br, 1H), 9.45 (br.s, 3H), 9.30 (s, 2H), 8.61 (t, J = 6.6 Hz, 1H), 8.40 (d, J = 1.8 Hz, 1H), 8.09 (dd, J = 7.8, 1.8 Hz, 1H), 7.69 (d, J = 8.7 Hz, 1H), 7.38 (d, J = 7.8 Hz, 1H), 7.30-7.15 (m, 3H), 7.20-7.05 (m, 3H), 5.05 (s, 2H), 4.09 (s, 3H), 3.13 (d, J = 6.6 Hz, 2H), 0.97 (s, 9H).

Example 40(74)

Benzyl 2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-[[1(S)-(2-benzoyloxycarbonylaminoethyl)-3-methylbutyl]carbamoyl]benzoate

[0712]



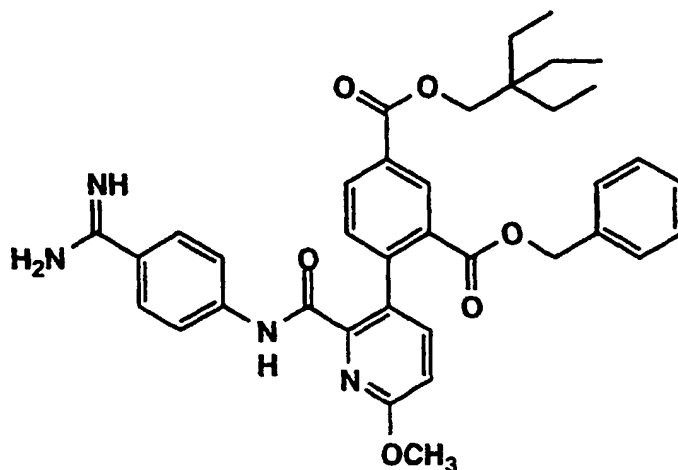
TLC : Rf 0.32 (Chloroform : Methanol : Water = 8 : 2 : 0.2) ;

NMR (300 MHz, CD₃OD) : δ 8.51 (d, J = 2.0 Hz, 1H), 8.02 (dd, J = 8.0, 2.0 Hz, 1H), 7.83 (d, J = 9.0 Hz, 2H), 7.76 (d, J = 9.0 Hz, 2H), 7.54 (d, J = 8.0 Hz, 1H), 7.33-7.16 (m, 9H), 7.09-7.06 (m, 2H), 6.99 (d, J = 8.0 Hz, 1H), 5.15-5.00 (m, 4H), 4.27 (m, 1H), 4.06 (s, 3H), 3.34-3.07 (m, 2H), 1.85-1.30 (m, 5H), 0.95 (d, J = 6.3 Hz, 6H).

Example 40(75)

Benzy 2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-[(2, 2-diethylbutyloxy)carbamoyl]benzoate

[0713]



TLC : Rf 0.54 (Chloroform : Methanol : Water = 8 : 2 : 0.2) ;

NMR (200 MHz, CD₃OD) : δ 8.68 (d, J = 1.8 Hz, 1H), 8.19 (d, J = 8.0, 1.8 Hz, 1H), 7.85 (d, J = 8.8 Hz, 2H), 7.77 (d, J = 8.8 Hz, 2H), 7.56 (d, J = 8.6 Hz, 1H), 7.36 (d, J = 8.0 Hz, 1H), 7.28-7.18 (m, 3H), 7.13-7.08 (m, 2H), 6.99 (d, J = 8.6 Hz, 1H), 5.09 (d, J = 12.0 Hz, 1H), 4.97 (d, J = 12.0 Hz, 1H), 4.16 (s, 2H), 4.08 (s, 3H), 1.43 (q, J = 7.6 Hz, 6H), 0.88 (t, J = 7.6 Hz, 9H).

Example 40(76)

Benzyl 2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-[(2, 2-dimethyl-3-hydroxypropyl)carbamoyl]benzoate

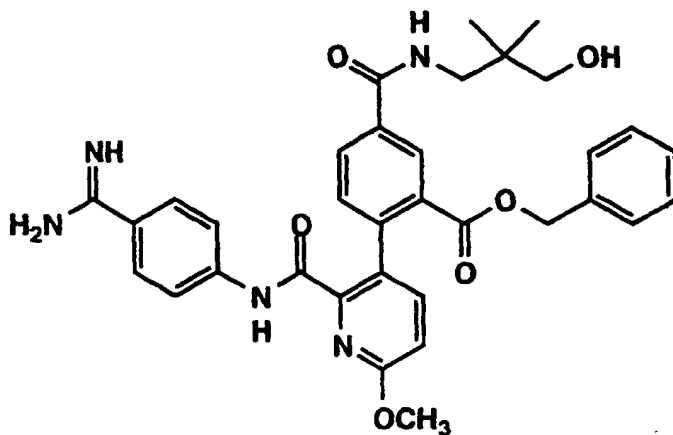
5 [0714]

10

15

20

25



30

TLC : Rf 0.29 (Chloroform : Methanol : Water = 8 : 2 : 0.1) ;

NMR (200 MHz, CD₃OD) : δ 8.51 (d, J = 2.0 Hz, 1H), 8.03 (dd, J = 8.0, 2.0 Hz, 1H), 7.84 (d, J = 9.2 Hz, 2H), 7.76 (d, J = 9.2 Hz, 2H), 7.55 (d, J = 8.4 Hz, 1H), 7.33 (d, J = 8.0 Hz, 1H), 7.23-7.17 (m, 3H), 7.10-7.05 (m, 2H), 6.99 (d, J = 8.4 Hz, 1H), 5.03 (d, J = 8.8 Hz, 2H), 4.06 (s, 3H), 3.34-3.28 (m, 4H), 0.96 (s, 6H).

Example 40(77)

Benzyl 2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-[(2, 2-diethylbutyl)carbamoyl]benzoate

35

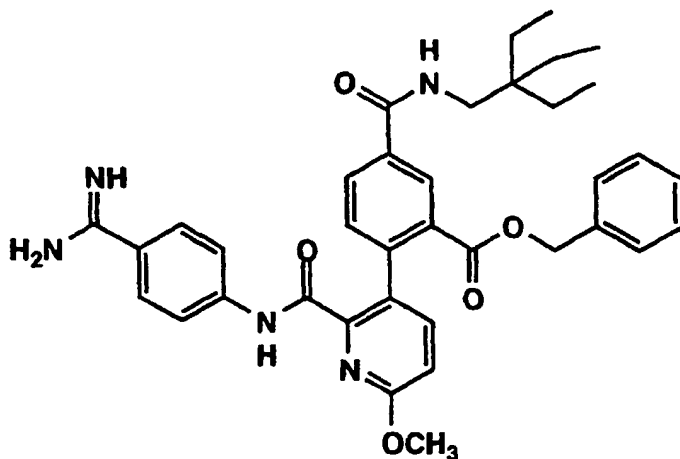
[0715]

40

45

50

55



EP 1 078 917 A1

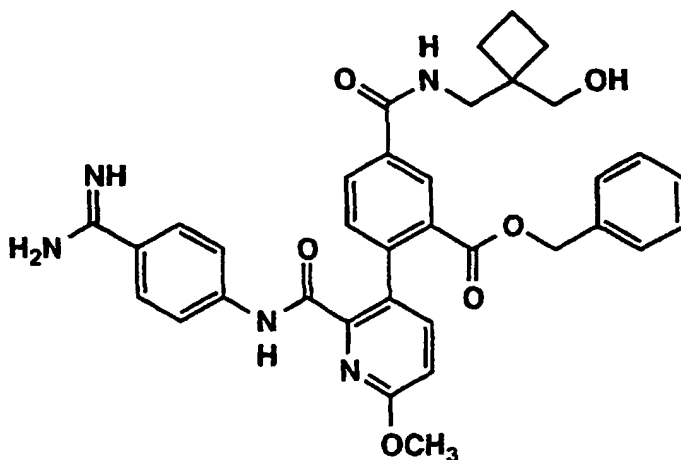
TLC : Rf 0.56 (Chloroform : Methanol : Water = 8 : 2 : 0.2) ;

NMR (300 MHz, CD₃OD) : δ 8.45 (d, J = 1.8 Hz, 1H), 7.97 (dd, J = 8.1, 1.8 Hz, 1H), 7.83 (d, J = 9.0 Hz, 2H), 7.78 (d, J = 9.0 Hz, 2H), 7.53 (d, J = 8.4 Hz, 1H), 7.31 (d, J = 8.1 Hz, 1H), 7.25-7.17 (m, 3H), 7.09-7.07 (m, 2H), 6.98 (d, J = 8.4 Hz, 1H), 5.07 (d, J = 11.4 Hz, 1H), 4.97 (d, J = 11.4 Hz, 1H), 4.06 (s, 3H), 3.35 (s, 2H), 1.33 (q, J = 7.5 Hz, 6H), 0.88 (t, J = 7.5 Hz, 9H).

Example 40(78)

Benzyl 2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-[[[(1-hydroxymethyl)cyclobutyl(methyl)carbamoyl]benzoate

[0716]



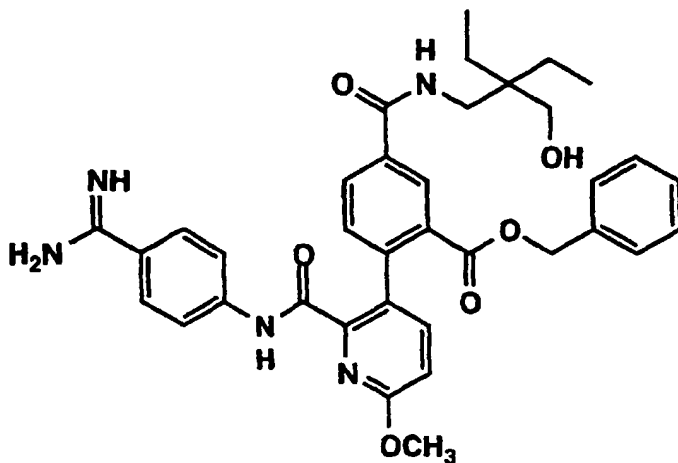
TLC : Rf 0.30 (Chloroform : Methanol : Water = 8 : 2 : 0.1) ;

NMR (300 MHz, CD₃OD) : δ 8.50 (d, J = 1.8 Hz, 1H), 8.01 (dd, J = 7.8, 1.8 Hz, 1H), 7.83 (d, J = 9.0 Hz, 2H), 7.77 (d, J = 9.0 Hz, 2H), 7.54 (dd, J = 8.4, 1.8 Hz, 1H), 7.32 (d, J = 7.8 Hz, 1H), 7.24-7.17 (m, 3H), 7.08-7.06 (m, 2H), 6.99 (dd, J = 8.4, 1.8 Hz, 1H), 5.02 (br d, J = 16.5 Hz, 2H), 4.06 (s, 3H); 3.57 (s, 2H), 3.56 (s, 2H), 1.93-1.82 (m, 6H).

Example 40(79)

Benzyl 2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-[(2-ethyl-2-hydroxymethylbutyl)carbamoyl]benzoate

[0717]



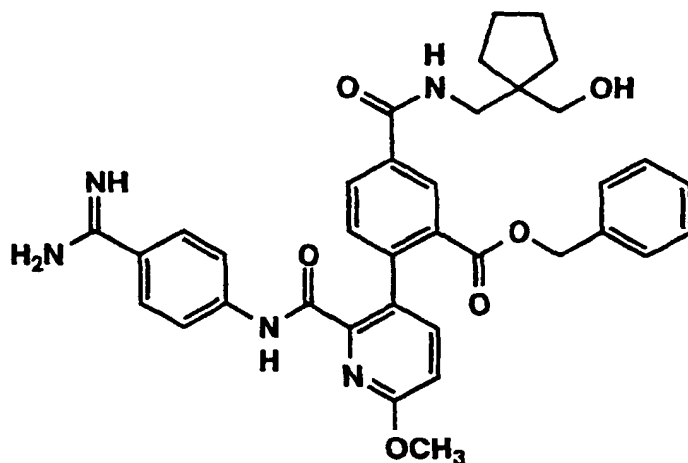
TLC : Rf 0.31 (Chloroform : Methanol : Water = 8 : 2 : 0.1) ;

NMR (300 MHz, CD₃OD) : δ 8.50 (d, J = 1.8 Hz, 1H), 8.01 (dd, J = 8.1, 1.8 Hz, 1H), 7.83 (d, J = 9.0 Hz, 2H), 7.77 (d, J = 9.0 Hz, 2H), 7.55 (d, J = 8.4 Hz, 1H), 7.33 (d, J = 8.1 Hz, 1H), 7.24-7.17 (m, 3H), 7.08-7.06 (m, 2H), 6.99 (d, J = 8.4 Hz, 1H), 5.02 (br d, J = 17.4 Hz, 2H), 4.06 (s, 3H), 3.36 (s, 2H), 3.35 (s, 2H), 1.35 (septet, J = 7.5 Hz, 4H), 0.90 (t, J = 7.5 Hz, 6H).

Example 40(80)

Benzyl 2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-[[[(1-hydroxymethyl)cyclopentylmethyl]carbamoyl]benzoate

[0718]



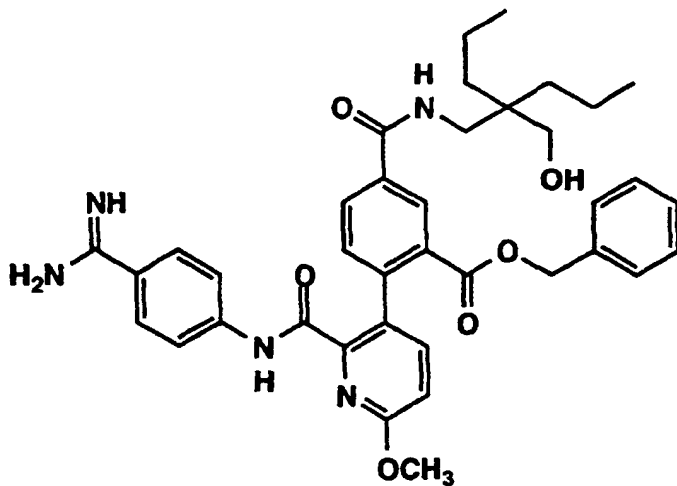
TLC : Rf 0.28 (Chloroform : Methanol : Water = 8 : 2 : 0.1) ;

NMR (300 MHz, CD₃OD) : δ 8.50 (d, J = 1.8 Hz, 1H), 8.02 (dd, J = 8.1, 1.8 Hz, 1H), 7.83 (d, J = 9.3 Hz, 2H), 7.77 (d, J = 9.3 Hz, 2H), 7.54 (d, J = 8.4 Hz, 1H), 7.33 (d, J = 8.1 Hz, 1H), 7.25-7.16 (m, 3H), 7.09-7.06 (m, 2H), 6.99 (d, J = 8.4 Hz, 1H), 5.02 (d, J = 16.8 Hz, 2H), 4.06 (s, 3H), 3.44 (s, 2H), 3.39 (s, 2H), 1.80-1.60 (m, 4H), 1.60-1.40 (m, 2H).

Example 40(81)

Benzyl 2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-[(2-propyl-2-hydroxymethylpentyl)carbamoyl]benzoate

[0719]



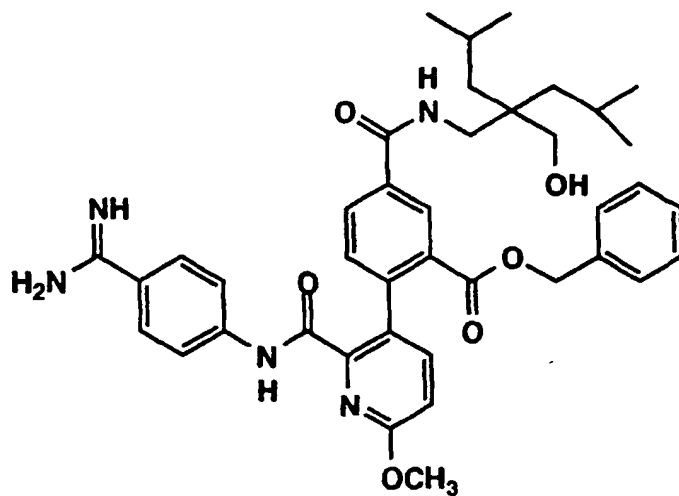
TLC : Rf 0.60 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (300 MHz, CD₃OD) : δ 8.49 (d, J = 1.8 Hz, 1H), 8.00 (dd, J = 8.1, 1.8 Hz, 1H), 7.85-7.75 (m, 4H), 7.55 (d, J = 8.7 Hz, 1H), 7.32 (d, J = 8.1 Hz, 1H), 7.23-7.20 (m, 3H), 7.09-7.06 (m, 2H), 6.99 (d, J = 8.7 Hz, 1H), 5.02 (d, J = 17.4 Hz, 2H), 4.06 (s, 3H), 3.60 (m, 1H), 3.39-3.25 (m, 3H), 1.40-1.20 (m, 8H), 0.93 (t, J = 6.9 Hz, 6H).

Example 40(82)

Benzyl 2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-[(2-(2-methylpropyl)-2-hydroxymethyl-4-methyl-

[0720]



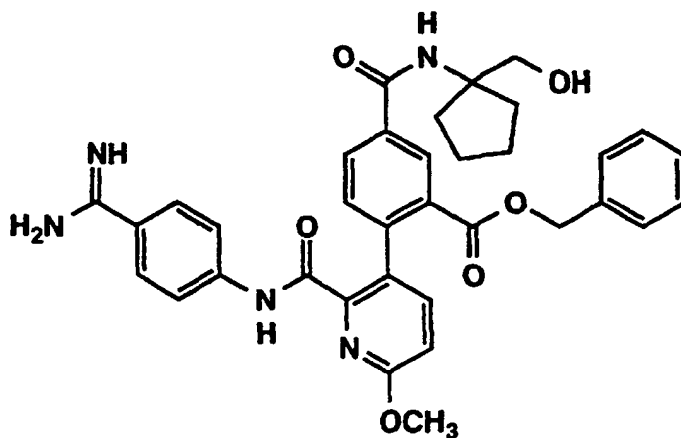
TLC : Rf 0.38 (Chloroform : Methanol : Water = 8 : 2 : 0.2) ;

NMR (300 MHz, CD₃OD) : δ 8.49 (d, J = 2.1 Hz, 1H), 8.00 (dd, J = 8.1, 2.1 Hz, 1H), 7.83 (d, J = 9.0 Hz, 2H), 7.77 (d, J = 9.0 Hz, 2H), 7.55 (d, J = 8.7 Hz, 1H), 7.34 (d, J = 8.1 Hz, 1H), 7.24-7.20 (m, 3H), 7.09-7.06 (m, 2H), 6.99 (d, J = 8.7 Hz, 1H), 5.15-4.95 (m, 2H), 4.07 (s, 3H), 3.49 (s, 2H), 3.45 (s, 2H), 1.86-1.76 (m, 2H), 1.50-1.30 (m, 4H), 0.98 (d, J = 6.6 Hz, 12H).

Example 40(83)

Benzyl 2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-[(1-hydroxy methylcyclopentyl)carbamoyl]benzoate

5 [0721]



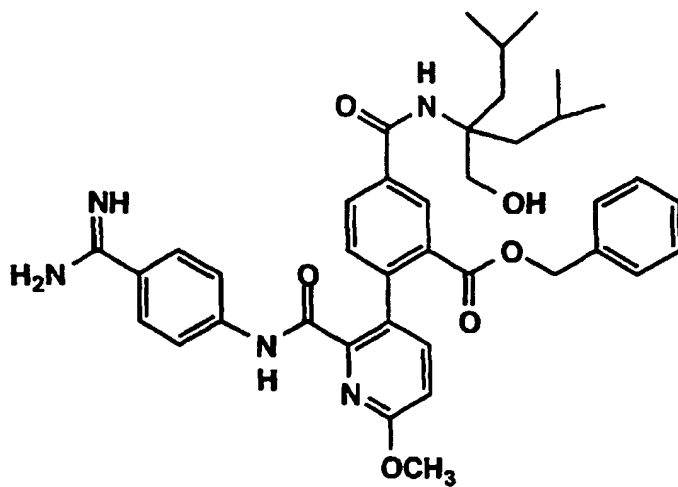
TLC : Rf 0.38 (Chloroform : Methanol : Water = 8 : 2 : 0.2) ;

NMR (300 MHz, CD₃OD) : δ 8.45 (d, J = 2.1 Hz, 1H), 7.98 (dd, J = 7.8, 2.1 Hz, 1H), 7.83 (d, J = 9.0 Hz, 2H), 7.77 (d, J = 9.0 Hz, 2H), 7.53 (d, J = 8.4 Hz, 1H), 7.29 (d, J = 7.8 Hz, 1H), 7.25-7.17 (m, 3H), 7.09-7.06 (m, 2H), 6.98 (d, J = 8.4 Hz, 1H), 5.15-4.90 (m, 2H), 4.60 (s, 3H), 3.80 (s, 2H), 2.18-2.01 (m, 2H), 1.96-1.70 (m, 4H), 1.70-1.52 (m, 2H).

Example 40(84)

Benzyl 2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-[(1-(2-methylpropyl)-1-hydroxymethyl-3-methyl-butyl)carbamoyl]benzoate

[0722]



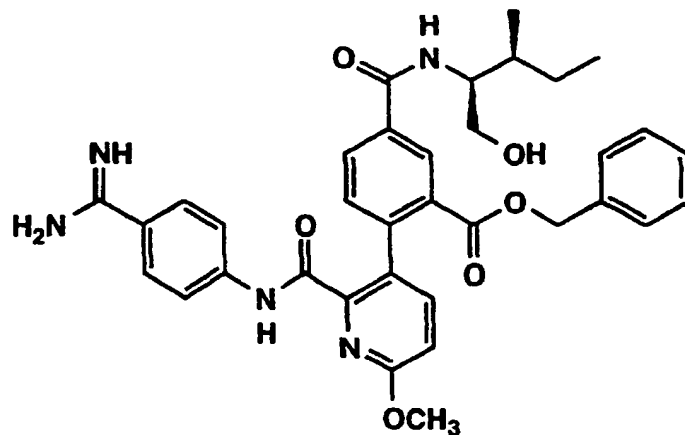
TLC : Rf 0.38 (Chloroform : Methanol : Water = 8 : 2 : 0.2) ;

NMR (300 MHz, CD₃OD) : δ 8.42 (d, J = 2.1 Hz, 1H), 7.93 (dd, J = 7.8, 2.1 Hz, 1H), 7.83 (d, J = 9.0 Hz, 2H), 7.78 (d, J = 9.0 Hz, 2H), 7.53 (d, J = 8.4 Hz, 1H), 7.30 (d, J = 7.8 Hz, 1H), 7.23-7.18 (m, 3H), 7.09-7.06 (m, 2H), 6.98 (d, J = 8.4 Hz, 1H), 5.15-4.90 (m, 2H), 4.06 (s, 3H), 3.80 (s, 2H), 1.92-1.76 (m, 6H), 0.99 (d, J = 6.0 Hz, 6H), 0.98 (d, J = 6.3 Hz, 6H).

Example 40(85)

Benzyl 2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-[(1(S)-(hydroxymethyl)-2(S)-methylbutyl)carbamoyl]benzoate

[0723]



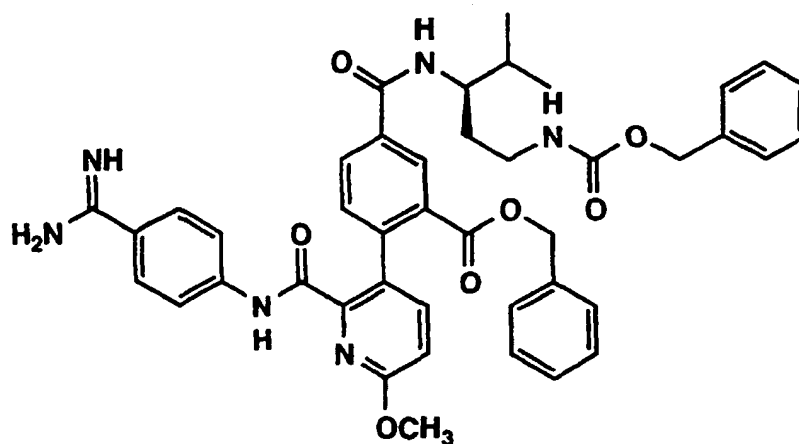
TLC : Rf 0.20 (Chloroform : Methanol : Acetic acid = 10 : 1 : 0.5) ;

NMR (300 MHz, CD₃OD) : δ 8.52 (d, J = 1.8 Hz, 1H), 8.04 (dd, J = 7.8, 1.8 Hz, 1H), 7.83 (d, J = 9.0 Hz, 2H), 7.77 (d, J = 9.0 Hz, 2H), 7.55 (d, J = 8.4 Hz, 1H), 7.32 (d, J = 7.8 Hz, 1H), 7.30-7.03 (m, 5H), 6.98 (d, J = 8.4 Hz, 1H), 5.03 (d, J = 15.6 Hz, 2H), 4.06 (s, 3H), 4.03 (m, 1H), 3.78 (m, 2H), 1.80 (m, 1H), 1.60 (m, 1H), 1.23 (m, 1H), 1.00 (d, J = 6.9 Hz, 3H), 0.95 (t, J = 7.5 Hz, 3H).

Example 40(86)

Benzyl 2-[2-(4-amidinophenylcarbamoyl)-6-ethoxy-3-pyridyl]-5-[(1S)-isopropyl-3-benzyloxycarbonylamino-3-propyl]carbamoyl]benzoate

[0724]



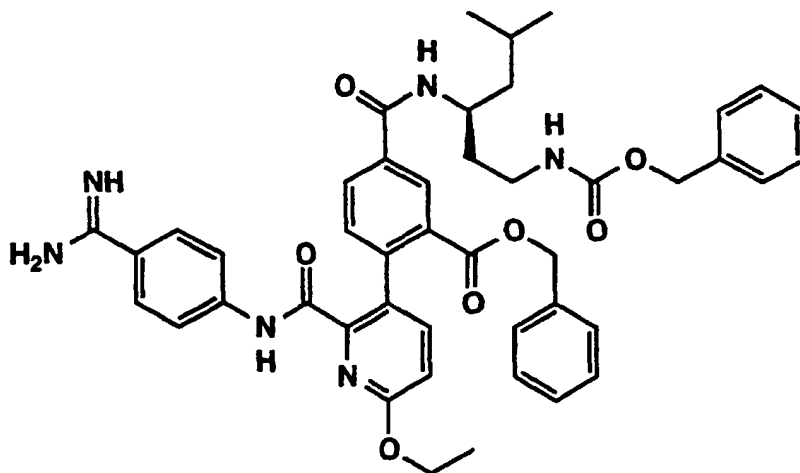
TLC : Rf 0.40 (Chloroform : Methanol : Acetic acid = 10 : 1 : 0.5) ;

NMR (200 MHz, CD₃OD) : δ 8.51 (d, J = 1.8 Hz, 1H), 8.05 (m, 1H), 7.81-7.77 (m, 4H), 7.50 (d, J = 8.4 Hz, 1H), 7.39-7.02 (m, 11H), 6.93 (d, J = 8.4 Hz, 1H), 5.02 (m, 4H), 4.46 (dd, J = 14.0, 7.4 Hz, 2H), 3.95 (m, 1H), 3.69 (m, 1H), 3.10 (m, 1H), 1.83 (m, 2H), 1.70 (m, 1H), 1.48 (t, J = 7.0 Hz, 3H), 0.97 (d, J = 7.0 Hz, 6H).

Example 40(87)

Benzyl 2-[2-(4-amidinophenylcarbamoyl)-6-ethoxy-3-pyridyl]-5-[(1S)-(2-benzoyloxycarbonylaminoethyl)-3-methylbutyl]carbamoylbenzoate

[0725]



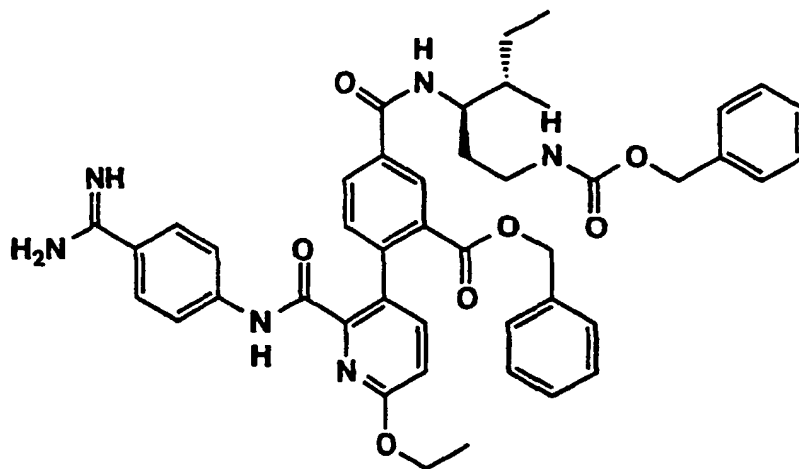
TLC : Rf 0.27 (Chloroform : Methanol : Acetic acid = 20 : 2 : 1) ;

NMR (300 MHz, CD₃OD) : δ 8.51 (d, J = 2.0 Hz, 1H), 8.02 (dd, J = 8.0, 2.0 Hz, 1H), 7.81 (d, J = 9.0 Hz, 2H), 7.76 (d, J = 9.0 Hz, 2H), 7.53 (d, J = 8.4 Hz, 1H), 7.36-7.16 (m, 9H), 7.10-7.05 (m, 2H), 6.96 (d, J = 8.4 Hz, 1H), 5.07 (brd, J = 12 Hz, 1H), 5.05 (s, 2H), 4.98 (brd, J = 12 Hz, 1H), 4.52-4.42 (m, 2H), 4.33-4.20 (m, 1H), 3.36-3.25 (m, 1H), 3.20-3.05 (m, 1H), 1.90-1.50 (m, 4H), 1.48 (t, J = 7.2 Hz, 3H), 1.42-1.30 (m, 1H), 0.95 (d, J = 6.0 Hz, 6H).

Example 40(88)

Benzyl 2-[2-(4-amidinophenylcarbamoyl)-6-ethoxy-3-pyridyl]-5-[(1(S)-(2-benzylloxycarbonylaminoethyl)-2(S)-methylbutyl)carbamoyl]benzoate

[0726]



TLC : Rf 0.30 (Chloroform : Methanol : Acetic acid = 20 : 2 : 1) ;

NMR (300 MHz, CD₃OD) : δ 8.51 (d, J = 2.0 Hz, 1H), 8.02 (dd, J = 8.0, 2.0 Hz, 1H), 7.82 (d, J = 9.0 Hz, 2H), 7.76 (d, J = 9.0 Hz, 2H), 7.53 (d, J = 8.4 Hz, 1H), 7.36-7.16 (m, 9H), 7.12-7.05 (m, 2H), 6.97 (d, J = 8.4 Hz, 1H), 5.07 (brd, J = 12 Hz, 1H), 5.04 (s, 2H), 4.97 (brd, J = 12 Hz, 1H), 4.52-4.42 (m, 2H), 4.12-3.98 (m, 1H), 3.33-3.20 (m, 1H), 3.15-3.00 (m, 1H), 1.95-1.80 (m, 1H), 1.75-1.45 (m, 3H), 1.49 (t, J = 7.2 Hz, 3H), 1.30-1.18 (m, 1H), 0.97 (d, J = 6.6 Hz, 3H), 0.94 (t, J = 7.5 Hz, 3H).

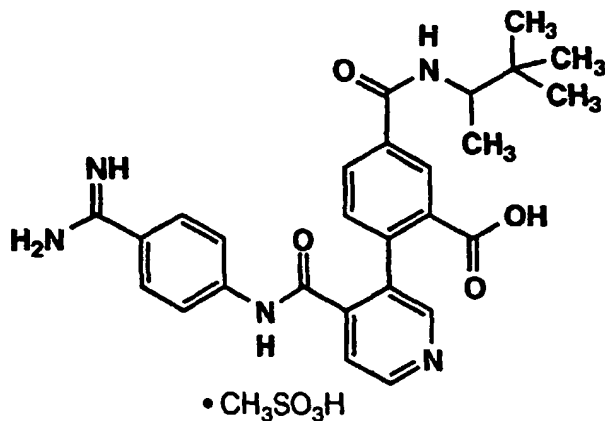
Example 41(1) — 41(90)

[0727] The following compounds were obtained by the same procedure as a series of reaction of Example 2, with the proviso that some compounds were not converted to salt thereof, or were converted to different salt thereof; using the compound prepared in Reference Example 40(1) — 40(88).

Example 41(1)

2-[4-(4-amidinophenylcarbamoyl)-3-pyridyl]-5-[(1, 2, 2-trimethylpropyl) carbamoyl]benzoic acid methanesulfonate

5 [0728]



25

TLC : R_f 0.35 (Chloroform : Methanol : Water = 7 : 3 : 0.3) ;

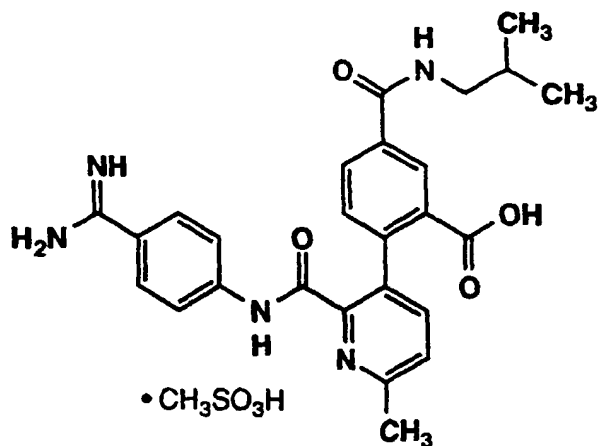
NMR (d₆-DMSO) : δ 11.05 (1H, s), 9.23 (2H, brs), 9.00 (2H, brs), 8.89 (1H, brd, J = 5.5 Hz), 8.70 (1H, s), 8.38 (1H, d, J = 2.0 Hz), 8.25 (1H, d, J = 9.0 Hz), 8.03 (1H, dd, J = 8.0 Hz, 2.0 Hz), 7.92 (1H, d, J = 5.5 Hz), 7.78 (2H, d, J = 9.0 Hz), 7.74 (2H, d, J = 9.0 Hz), 7.45 (1H, d, J = 8.0 Hz), 3.99 (1H, dq, J = 9.0 Hz, 7.0 Hz), 2.36 (3H, s), 1.08 (3H, d, J = 7.0 Hz), 0.89 (9H, s).

30

Example 41(2)

35 2-[2-(4-amidinophenylcarbamoyl)-6-methyl-3-pyridyl]-5-[(2-methylpropyl) carbamoyl]benzoic acid methanesulfonate

[0729]



40

45

50

55

EP 1 078 917 A1

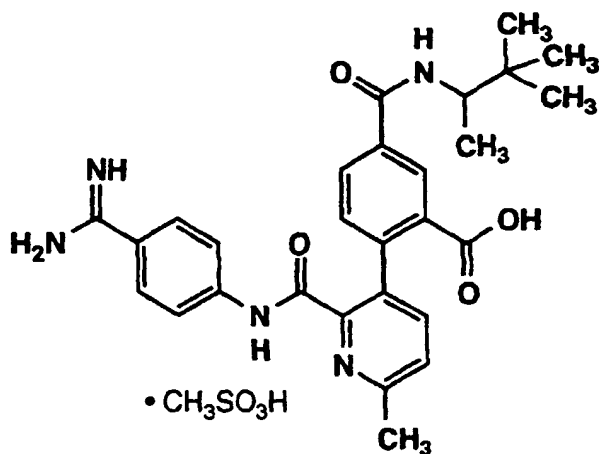
TLC : Rf 0.13 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d₆-DMSO) : δ 10.85 (1H, s), 9.21 (2H, brs), 8.96 (2H, brs), 8.71 (1H, brt, J = 5.5 Hz), 8.42 (1H, d, J = 2.0 Hz), 8.03 (1H, dd, J = 8.0 Hz, 2.0 Hz), 7.92 (2H, d, J = 8.5 Hz), 7.78 (2H, d, J = 8.5 Hz), 7.64 (1H, d, J = 8.0 Hz), 7.55 (1H, d, J = 8.0 Hz), 7.30 (1H, d, J = 8.0 Hz), 3.11 (2H, brt, J = 6.5 Hz), 2.67 (3H, s), 2.37 (3H, s), 1.94-1.80 (1H, m), 0.90 (6H, d, J = 6.5 Hz).

Example 41(3)

2-[2-(4-amidinophenylcarbamoyl)-6-methyl-3-pyridyl]-5-[(1, 2, 2-trimethylpropyl) carbamoyl]benzoic acid methanesulfonate

[0730]



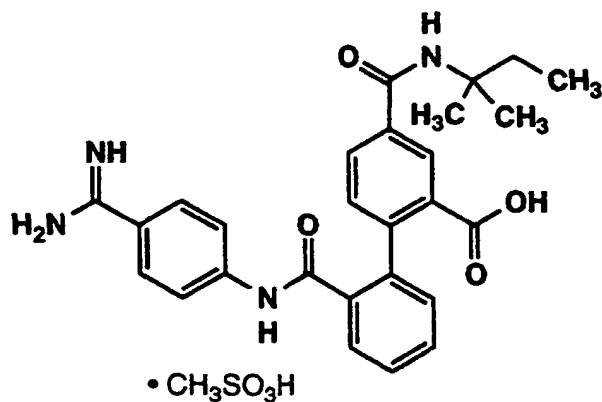
TLC : Rf 0.16 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d₆-DMSO) : δ 10.86 (1H, s), 9.22 (2H, brs), 8.98 (2H, brs), 8.38 (1H, d, J = 1.5 Hz), 8.23 (1H, brd, J = 9.0 Hz), 8.02 (1H, dd, J = 8.0 Hz, 1.5 Hz), 7.93 (2H, d, J = 8.5 Hz), 7.79 (2H, d, J = 8.5 Hz), 7.62 (1H, d, J = 8.0 Hz), 7.56 (1H, d, J = 8.0 Hz), 7.29 (1H, d, J = 8.0 Hz), 4.01 (1H, dq, J = 9.0 Hz, 7.0 Hz), 2.67 (3H, s), 2.38 (3H, s), 1.10 (3H, d, J = 7.0 Hz), 0.92 (9H, s).

Example 41(4)

2'-(4-amidinophenylcarbamoyl)-4-(1, 1-dimethylpropylcarbamoyl)-2-biphenylcarboxylic acid methanesulfonate

[0731]

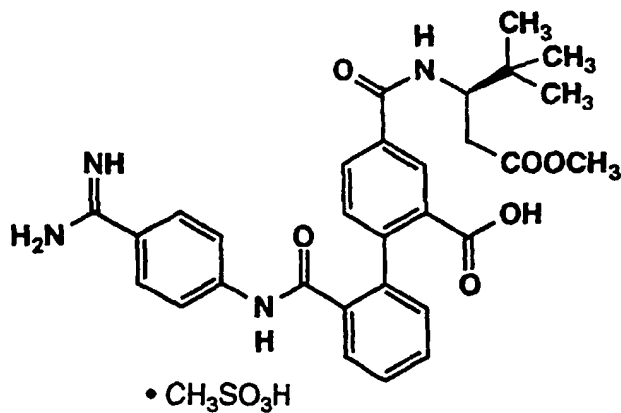
TLC : R_f 0.15 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d₆-DMSO) : δ 10.5 (1H, s), 9.15 (2H, br s), 8.84 (2H, br s), 8.20 (1H, d, J = 2.1 Hz), 7.90 (1H, dd, J = 2.1, 7.8 Hz), 7.81 (1H, s), 7.72 (4H, s), 7.72-7.67 (1H, m), 7.59-7.49 (2H, m), 7.28 (1H, d, J = 8.1 Hz), 7.26-7.23 (1H, m), 2.33 (3H, s), 1.77 (2H, q, J = 7.5 Hz), 1.31 (6H, s), 0.79 (3H, t, J = 7.5 Hz).

Example 41(5)

2'-(4-amidinophenylcarbamoyl)-4-[(1(S)-t-butyl-2-methoxycarbonylethyl) carbamoyl]-2-biphenylcarboxylic acid methanesulfonate

[0732]

TLC : R_f 0.18 (Chloroform : Methanol : Water = 10 : 2 : 1) ;

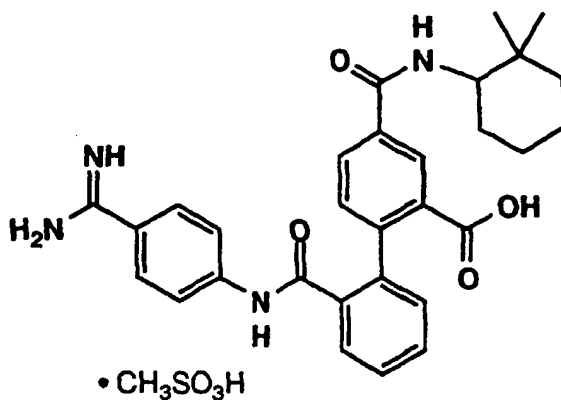
NMR (d₆-DMSO) : δ 10.6 (1H, s), 9.14 (2H, br s), 8.80 (2H, br s), 8.29 (1H, d, J = 9.3 Hz), 8.23 (1H, s), 7.90 (1H,

d, J = 8.8 Hz), 7.73-7.68 (5H, m), 7.60-7.48 (2H, m), 7.32-7.25 (2H, m), 4.28 (1H, t, J = 8.8 Hz), 3.51 (3H, s), 2.72-2.40 (2H, m), 2.30 (3H, s), 0.89 (9H, s).

Example 41(6)

2'-(4-amidinophenylcarbamoyl)-4-(2, 2-dimethylcyclohexylcarbamoyl)-2-biphenylcarboxylic acid methanesulfonate

[0733]

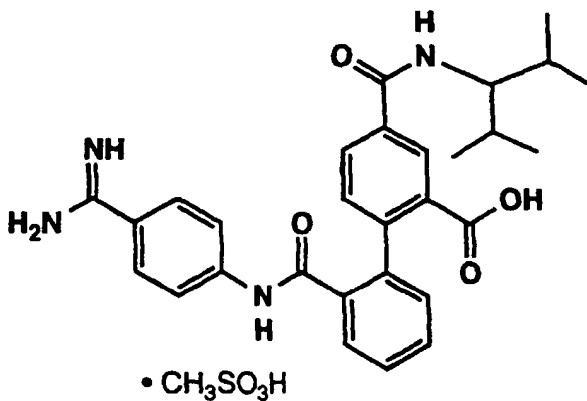


TLC : R_f 0.36 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;
 NMR (d₆-DMSO) : δ 13.0-12.0 (1H, br), 10.56 (1H, s), 9.16 (2H, s), 8.89 (2H, s), 8.25 (1H, d, J = 2.0 Hz), 8.10 (1H, d, J = 9.0 Hz), 7.94 (1H, dd, J = 2.0, 8.0 Hz), 7.73 (4H, like s), 7.69 (1H, dd, J = 2.0, 8.0 Hz), 7.5-7.45 (2H, m), 7.30 (1H, d, J = 8.0 Hz), 7.25 (1H, dd, J = 2.0, 8.0 Hz), 3.81 (1H, m), 2.36 (3H, s), 1.8-1.6 (1H, m), 1.7-1.3 (4H, m), 1.4-1.2 (3H, m), 0.89 (3H, s), 0.84 (3H, s).

Example 41(7)

2'-(4-amidinophenylcarbamoyl)-4-(1-isopropyl-2-methylpropylcarbamoyl)-2-biphenylcarboxylic acid methanesulfonate

[0734]



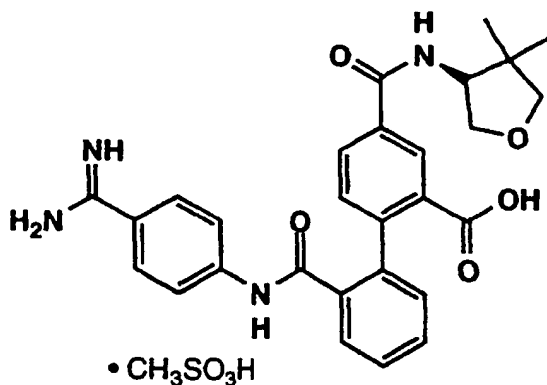
TLC : Rf 0.31 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d_6 -DMSO) : 10.57 (1H, s), 9.15 (2H, s), 8.81 (2H, s), 8.29 (1H, d, J = 2.0 Hz), 8.02 (1H, d, J = 10.0 Hz), 7.97 (1H, dd, J = 2.0, 8.0 Hz), 7.74 (4H, s), 7.71 (1H, dd, J = 2.0, 8.0 Hz), 7.58 (1H, dt, J = 2.0, 8.0 Hz), 7.54 (1H, dt, J = 2.0, 8.0 Hz), 7.32 (1H, d, J = 8.0 Hz), 7.27 (1H, dd, J = 2.0, 8.0 Hz), 3.67 (1H, dt, J = 7.2, 10.0 Hz), 2.33 (3H, s), 1.91 (2H, m), 0.87 (6H, d, J = 7.5 Hz), 0.85 (6H, d, J = 7.5 Hz).

Example 41(8)

2'-(4-amidinophenylcarbamoyl)-4-[(4, 4-dimethyloxolan-3(S)-yl)carbamoyl]-2-biphenylcarboxylic acid methanesulfonate

[0735]



TLC : Rf 0.15 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d_6 -DMSO) : δ 10.5 (s, 1H), 9.14 (br s, 2H), 8.78 (br s, 2H), 8.51 (d, J = 8.8 Hz, 1H), 8.31 (d, J = 1.4 Hz, 1H), 7.98 (dd, J = 8.0, 1.4 Hz, 1H), 7.72-7.68 (m, 5H), 7.60-7.50 (m, 2H), 7.32 (d, J = 8.0 Hz, 1H), 7.30-7.25 (m, 1H), 7.30-7.25 (m, 1H), 4.40-4.25 (m, 1H), 4.12-4.03 (m, 1H), 3.70-3.60 (m, 1H), 3.54-3.39 (m, 2H), 2.29 (s, 3H), 1.08 (s, 3H), 0.93 (s, 3H).

Example 41(9)

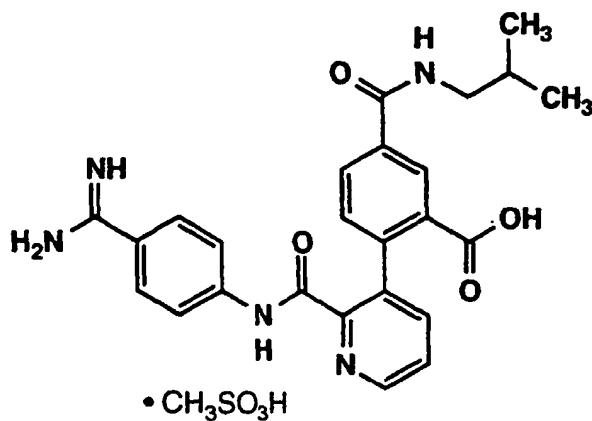
2-[2-(4-amidinophenylcarbamoyl)-3-pyridyl]-5-[(2-methylpropyl)carbamoyl] benzoic acid methanesulfonate

5 [0736]

10

15

20



25

TLC : R_f 0.34 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d₆-DMSO) : δ 11.00 (s, 1H), 9.12 (s, 2H), 8.92 (s, 2H), 8.73 (dd, J = 4.8, 2.1 Hz, 1H), 8.71 (br.d, J = 6.3 Hz, 1H), 8.43 (d, J = 1.8 Hz, 1H), 8.05 (dd, J = 7.8, 1.8 Hz, 1H), 7.95 (d, J = 9.0 Hz, 2H), 7.8-7.7 (m, 1H), 7.77 (d, J = 9.0 Hz, 2H), 7.71 (dd, J = 7.8, 4.8 Hz, 1H), 7.34 (d, J = 7.8 Hz, 1H), 5.0-4.2 (br, 1H), 3.12 (t, J = 6.3 Hz, 2H), 2.36 (s, 3H), 1.88 (like septet, J = 6.3 Hz, 1H), 0.91 (d, J = 6.3 Hz, 6H).

30

Example 41(10)

2-[2-(4-amidinophenylcarbamoyl)-6-methyl-3-pyridyl]-5-[(3-hydroxymethyl-2, 2-dimethylpropyl)carbamoyl]benzoic acid methanesulfonate

35

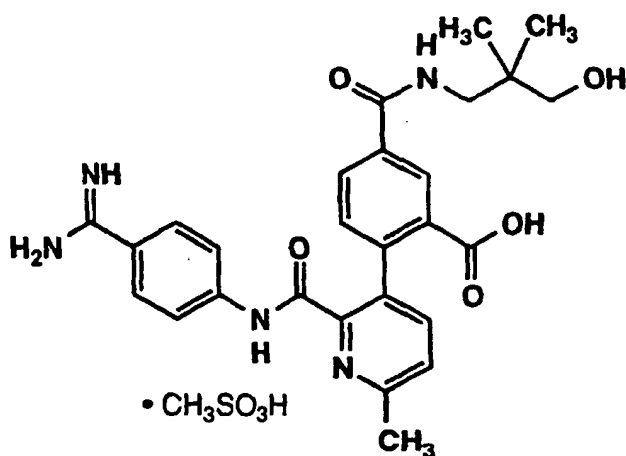
[0737]

40

45

50

55



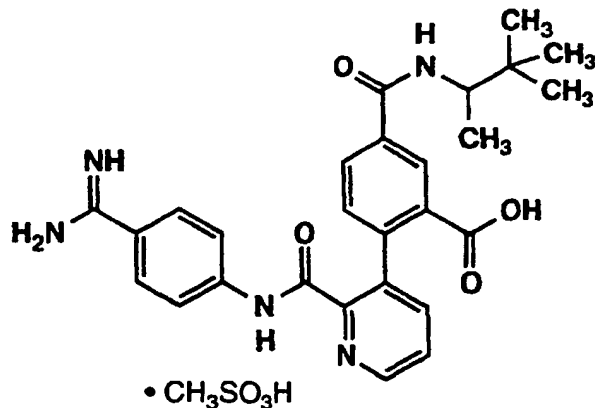
TLC : Rf 0.25 (Chloroform : Methanol : Water = 7 : 3 : 0.3) ;

NMR (d_6 -DMSO) : δ 10.86 (s, 1H), 9.22 (brs, 2H), 8.97 (brs, 2H), 8.66 (brt, J = 6.5 Hz, 1H), 8.41 (d, J = 1.8 Hz, 1H),
 8.04 (dd, J = 8.0, 1.8 Hz, 1H), 7.93 (d, J = 8.7 Hz, 2H), 7.79 (d, J = 8.7 Hz, 2H), 7.64 (d, J = 8.0 Hz, 1H), 9.56 (d, J
 = 8.0 Hz, 1H), 7.31 (d, J = 8.0 Hz, 1H), 3.19 (d, J = 6.5 Hz, 2H), 3.15 (s, 2H), 2.67 (s, 3H), 2.38 (s, 3H), 0.84 (s, 6H).

Example 41(11)

2-[2-(4-amidinophenylcarbamoyl)-3-pyridyl]-5-[(1, 2, 2-trimethylpropyl) carbamoyl]benzoic acid methanesulfonate

[0738]



TLC : Rf 0.36 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d_6 -DMSO) : δ 11.00 (s, 1H), 9.20 (br.s, 2H), 8.93 (br.s, 2H), 8.73 (dd, J = 4.8, 2.1 Hz, 1H), 8.40 (d, J = 1.8
 Hz, 1H), 8.25 (d, J = 9.6 Hz, 1H), 8.04 (dd, J = 7.8, 1.8 Hz, 1H), 7.95 (d, J = 9.0 Hz, 2H), 7.77 (d, J = 9.0 Hz, 2H),
 7.75-7.65 (m, 2H), 7.33 (d, J = 7.8 Hz, 1H), 6.5-5.0 (br, 1H), 4.01 (m, 1H), 2.36 (s, 3H), 1.11 (d, J = 6.6 Hz, 3H),
 0.92 (s, 9H).

Example 41(12)

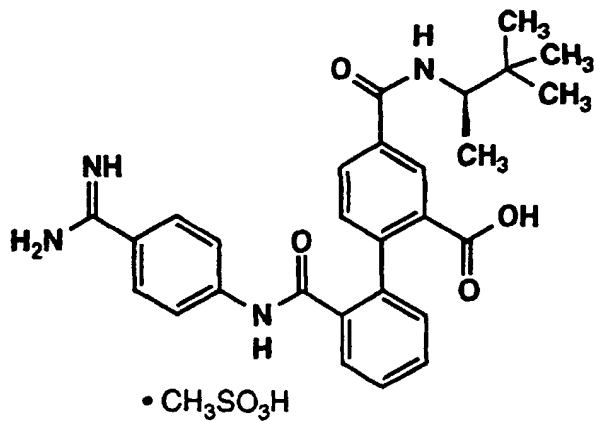
2'-(4-amidinophenylcarbamoyl)-4-[(1(R), 2, 2-trimethylpropyl)carbamoyl]-2-biphenylcarboxylic acid methanesulfonate

5 [0739]

10

15

20



25

TLC : R_f 0.14 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;
 NMR (d₆-DMSO) : δ 10.6 (s, 1H), 9.15 (br s, 2H), 8.85 (br s, 2H), 8.26 (d, J = 1.8 Hz, 1H), 8.18 (d, J = 8.6 Hz, 1H),
 7.95 (dd, J = 8.0, 1.8 Hz, 1H), 7.73-7.58 (m, 5H), 7.60-7.48 (m, 2H), 7.30 (d, J = 8.2 Hz, 1H), 7.28-7.24 (m, 1H),
 4.05-3.90 (m, 1H), 2.33 (s, 3H), 1.07 (d, J = 6.8 Hz, 3H), 0.89 (s, 9H).

30

Example 41(13)

2'-(4-amidinophenylcarbamoyl)-4-[(1(S), 2, 2-trimethylpropyl)carbamoyl]-2-biphenylcarboxylic acid methanesulfonate

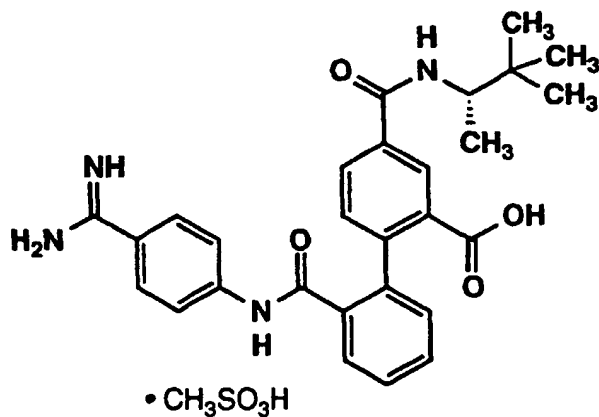
35

[0740]

40

45

50



55

TLC : R_f 0.14 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

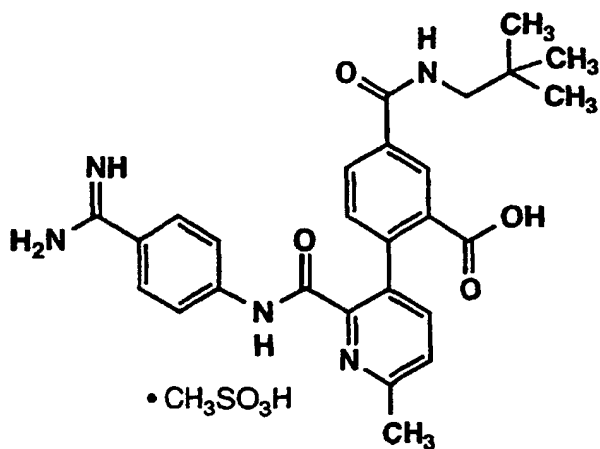
EP 1 078 917 A1

NMR (d_6 -DMSO) : δ 10.5 (s, 1H), 9.15 (br s, 2H), 8.83 (br s, 2H), 8.26 (d, J = 1.8 Hz, 1H), 8.17 (d, J = 9.2 Hz, 1H), 7.95 (dd, J = 8.0, 1.8 Hz, 1H), 7.73-7.67 (m, 5H), 7.60-7.48 (m, 2H), 7.30 (d, J = 8.2 Hz, 1H), 7.28-7.24 (m, 1H), 4.05-3.90 (m, 1H), 2.32 (s, 3H), 1.07 (d, J = 6.8 Hz, 3H), 0.89 (s, 9H).

5 Example 41(14)

2-[2-(4-amidinophenylcarbamoyl)-6-methyl-3-pyridyl]-5-[(2, 2-dimethylpropyl) carbamoyl]benzoic acid methanesulfonate

10 [0741]



TLC : R_f 0.15 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d_6 -DMSO) : δ 10.85 (s, 1H), 9.22 (brs, 2H), 8.97 (brs, 2H), 8.61 (brt, J = 6.5 Hz, 1H), 8.42 (d, J = 2.0 Hz, 1H), 8.04 (dd, J = 8.0, 2.0 Hz, 1H), 7.93 (d, J = 8.7 Hz, 2H), 7.79 (d, J = 8.7 Hz, 2H), 7.64 (d, J = 7.8 Hz, 1H), 7.55 (d, J = 7.8 Hz, 1H), 7.30 (d, J = 8.0 Hz, 1H), 3.13 (d, J = 6.5 Hz, 2H), 2.67 (s, 3H), 2.37 (s, 3H), 0.91 (s, 9H).

Example 41(15)

2-[2-(4-amidinophenylcarbamoyl)-6-methyl-3-pyridyl]-5-[(2, 2-dimethylpropyl) carbamoyl]benzoic acid

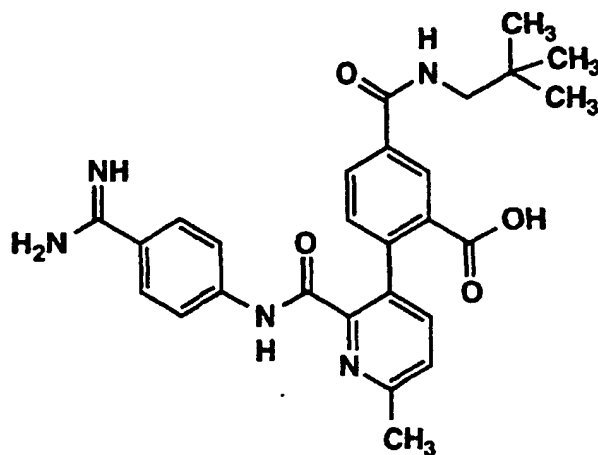
5 [0742]

10

15

20

25



30

TLC : Rf 0.49 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (300 MHz, DMSO-d₆) : δ 13.6 (brs, 1H), 9.01 (brs, 4H), 8.38 (brt, J = 6.3 Hz, 1H), 8.04 (d, J = 1.5 Hz, 1H), 7.64 (dd, J = 8.0, 1.5 Hz, 1H), 7.59 (s, 4H), 7.39 (d, J = 8.0 Hz, 1H), 7.35 (d, J = 8.0 Hz, 1H), 6.98 (d, J = 8.0 Hz, 1H), 3.05 (d, J = 6.3 Hz, 2H), 2.56 (s, 3H), 0.87 (s, 9H).

Example 41(16)

35 2-[2-(4-amidinophenylcarbamoyl)-6-methyl-3-pyridyl]-5-[(2, 2-dimethylpropyl) carbamoyl]benzoic acid dihydrochloride

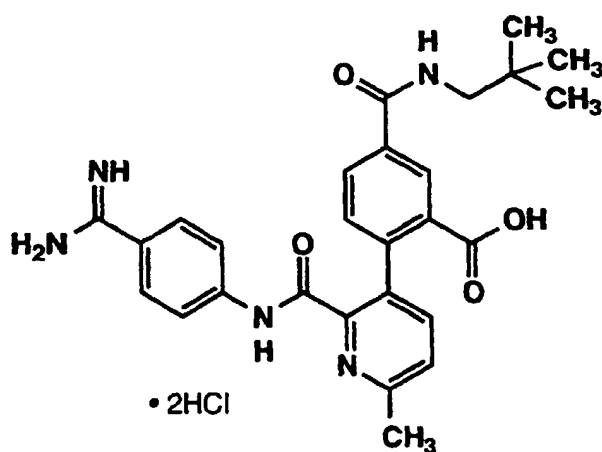
[0743]

40

45

50

55



EP 1 078 917 A1

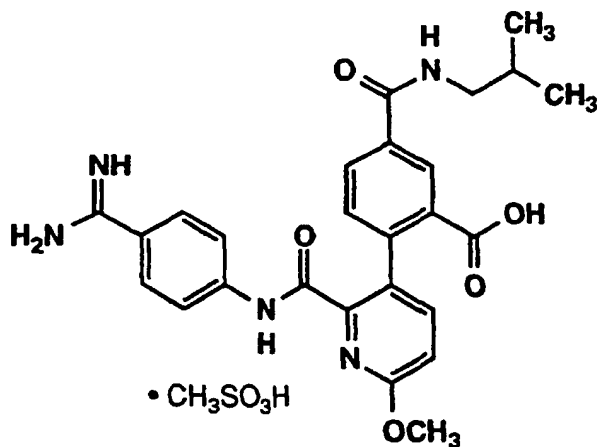
TLC : Rf 0.39 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (300 MHz, DMSO-d₆) : δ 10.85 (s, 1H), 9.26 (brs, 2H), 9.03 (brs, 2H), 8.61 (brt, J = 6.3 Hz, 1H), 8.41 (d, J = 1.8 Hz, 1H), 8.04 (dd, J = 8.0, 1.8 Hz, 1H), 7.93 (d, J = 8.7 Hz, 2H), 7.80 (d, J = 8.7 Hz, 2H), 7.63 (d, J = 8.0 Hz, 1H), 7.55 (d, J = 8.0 Hz, 1H), 7.30 (d, J = 8.0 Hz, 1H), 3.13 (d, J = 6.3 Hz, 2H), 2.67 (s, 3H), 0.91 (s, 9H).

Example 41(17)

2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-[(2-methylpropyl) carbamoyl]benzoic acid methanesulfonate

[0744]



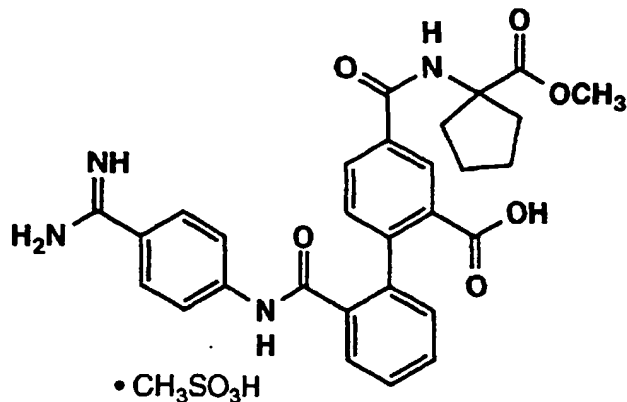
TLC : Rf 0.33 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d₆-DMSO) : δ 13.0-12.5 (broad, 1H), 10.61 (s, 1H), 9.21 (brs, 2H), 8.92 (brs, 2H), 8.70 (brt, J = 6.0 Hz, 1H), 8.41 (d, J = 1.8 Hz, 1H), 8.02 (dd, J = 8.0, 1.8 Hz, 1H), 7.90 (d, J = 9.0 Hz, 2H), 7.79 (d, J = 9.0 Hz, 2H), 7.65 (d, J = 8.4 Hz, 1H), 7.30 (d, J = 8.0 Hz, 1H), 7.12 (d, J = 8.4 Hz, 1H), 4.09 (s, 3H), 3.11 (t, J = 6.5 Hz, 2H), 2.34 (s, 3H), 1.94-1.80 (m, 1H), 0.90 (d, J = 6.5 Hz, 6H).

Example 41(18)

2'-[4-(4-amidinophenylcarbamoyl)-4-(1-methoxycarbonylcyclopentylcarbamoyl)-2-biphenylcarboxylic acid methanesulfonate

[0745]



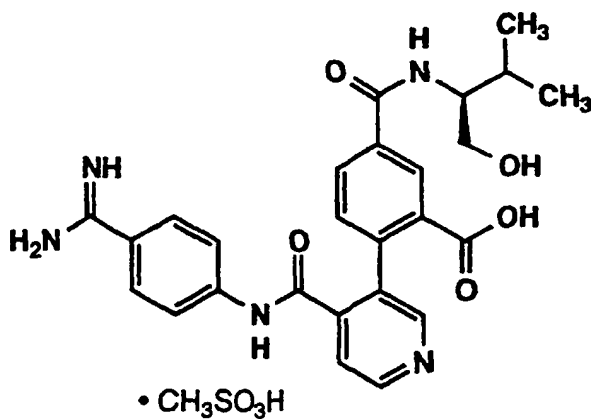
TLC : Rf 0.21 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d₆-DMSO) : δ 10.6 (s, 1H), 9.15 (br s, 2H), 8.87 (s, 1H), 8.83 (br s, 2H), 8.30 (d, J = 1.8 Hz, 1H), 7.97 (dd, J = 8.0, 1.8 Hz, 1H), 7.73-7.68 (m, 5H), 7.63-7.48 (m, 2H), 7.32 (d, J = 8.0 Hz, 1H), 7.30-7.24 (m, 1H), 3.57 (s, 3H), 2.32 (s, 3H), 2.20-2.00 (m, 4H), 1.80-1.60 (m, 4H).

Example 41(19)

2-[4-(4-amidinophenylcarbamoyl)-3-pyridyl]-5-[(1(S)-hydroxymethyl-2-methyl propyl)carbamoyl]benzoic acid methanesulfonate

[0746]



EP 1 078 917 A1

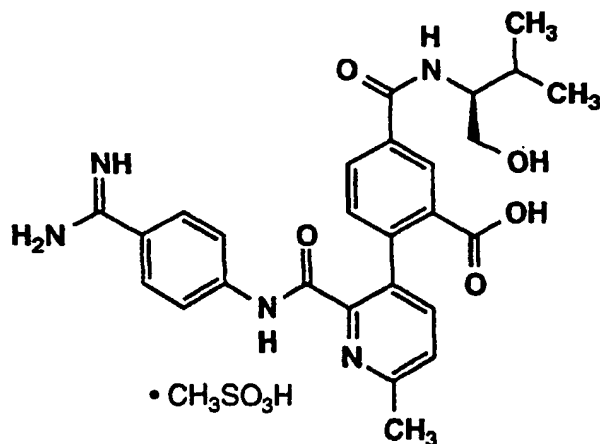
TLC : Rf 0.12 (Chloroform : Methanol : Water = 7 : 3 : 0.3) ;

NMR (d_6 -DMSO) : δ 11.04 (s, 1H), 9.23 (brs, 2H), 8.99 (brs, 2H), 8.88 (d, J = 5.4 Hz, 1H), 8.70 (s, 1H), 8.42 (d, J = 1.8 Hz, 1H), 8.28 (d, J = 9.0 Hz, 1H), 8.07 (dd, J = 8.0, 1.8 Hz, 1H), 7.90 (d, J = 5.4 Hz, 1H), 7.77 (d, J = 9.3 Hz, 2H), 7.73 (d, J = 9.3 Hz, 2H), 7.46 (d, J = 8.0 Hz, 1H), 3.86-3.76 (m, 1H), 3.56-3.45 (m, 2H), 2.36 (s, 3H), 1.98-1.82 (m, 1H), 0.90 (d, J = 6.9 Hz, 3H), 0.86 (d, J = 6.9 Hz, 3H).

Example 41(20)

2-[2-(4-amidinophenylcarbamoyl)-6-methyl-3-pyridyl]-5-[(1(S)-hydroxymethyl-2-methylpropyl)carbamoyl]benzoic acid
methanesulfonate

[0747]



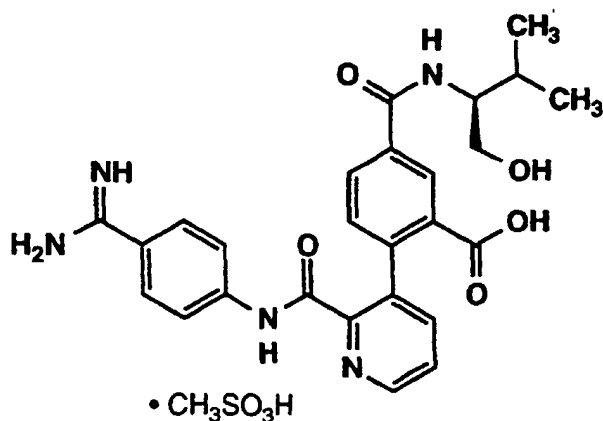
TLC : Rf 0.19 (Chloroform : Methanol : Water = 7 : 3 : 0.3) ;

NMR (d_6 -DMSO) : δ 10.85 (s, 1H), 9.22 (brs, 2H), 8.97 (brs, 2H), 8.43 (d, J = 1.8 Hz, 1H), 8.25 (d, J = 9.0 Hz, 1H), 8.06 (dd, J = 8.0, 1.8 Hz, 1H), 7.93 (d, J = 9.0 Hz, 2H), 7.79 (d, J = 9.0 Hz, 2H), 7.63 (d, J = 8.0 Hz, 1H), 7.55 (d, J = 8.0 Hz, 1H), 7.30 (d, J = 8.0 Hz, 1H), 3.90-3.80 (m, 1H), 3.58-3.48 (m, 2H), 2.67 (s, 3H), 2.37 (s, 3H), 2.01-1.86 (m, 1H), 0.92 (d, J = 6.9 Hz, 3H), 0.89 (d, J = 6.6 Hz, 3H).

Example 41(21)

2-[2-(4-amidinophenylcarbamoyl)-3-pyridyl]-5-[(1(S)-hydroxymethyl-2-methyl propyl)carbamoyl]benzoic acid methanesulfonate

[0748]



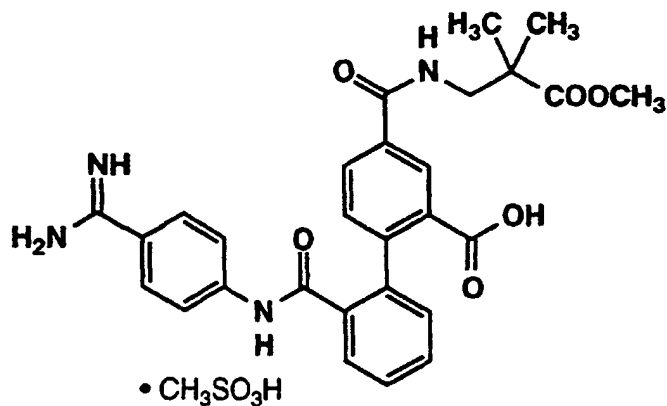
TLC : R_f 0.45 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d₆-DMSO) : δ 11.00 (s, 1H), 9.19 (s, 2H), 8.90 (s, 2H), 8.73 (dd, J = 4.5, 1.8 Hz, 1H), 8.44 (d, J = 1.8 Hz, 1H), 8.25 (br.d, J = 8.7 Hz, 1H), 8.08 (dd, J = 8.0, 1.8 Hz, 1H), 7.95 (d, J = 8.7 Hz, 2H), 7.76 (d, J = 8.7 Hz, 2H), 7.80-7.65 (m, 2H), 7.33 (d, J = 8.0 Hz, 1H), 4.80-4.20 (br, 2H), 3.86 (m, 1H), 3.60-3.50 (m, 2H), 2.34 (s, 3H), 1.94 (like sextet, J = 7.0 Hz, 1H), 0.93 (d, J = 7.0 Hz, 3H), 0.90 (d, J = 7.0 Hz, 3H).

Example 41(22)

2'-(4-amidinophenylcarbamoyl)-4-[(2-methoxycarbonyl-2,2-dimethylethyl)carbamoyl]-2-biphenylcarboxylic acid methanesulfonate

[0749]



EP 1 078 917 A1

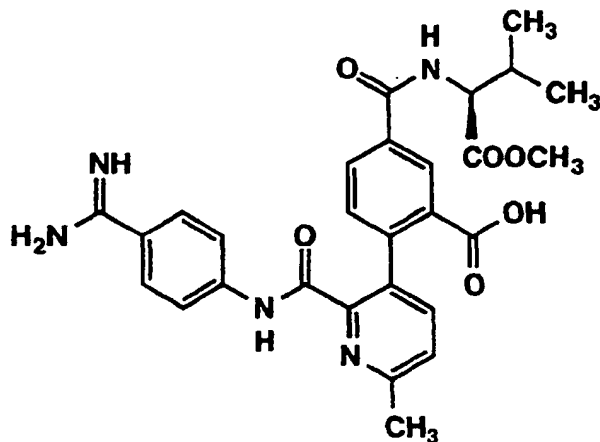
TLC : Rf 0.25 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (300 MHz, d₆-DMSO) : δ 10.6 (s, 1H), 9.15 (br s, 2H), 8.83 (br s, 2H), 8.61 (t, J = 6.3 Hz, 1H), 8.25 (d, J = 1.5 Hz, 1H), 7.92 (dd, J = 8.1, 1.5 Hz, 1H), 7.72-7.68 (m, 5H), 7.65-7.50 (m, 2H), 7.32 (d, J = 8.1 Hz, 1H), 7.27 (dd, J = 7.2, 1.5 Hz, 1H), 3.58 (s, 3H), 3.42 (d, J = 6.3 Hz, 2H), 2.31 (s, 3H), 1.13 (s, 6H).

Example 41(23)

2-[2-(4-amidinophenylcarbamoyl)-6-methyl-3-pyridyl]-5-[(1(S)-methoxycarbonyl-2-methylpropyl)carbamoyl]benzoic acid

[0750]



TLC : Rf 0.39 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (300 MHz, CD₃OD) : δ 8.51 (d, J = 1.8 Hz, 1H), 8.03 (dd, J = 8.0, 1.8 Hz, 1H), 7.88 (d, J = 9.0 Hz, 2H), 7.76 (d, J = 9.0 Hz, 2H), 7.61 (d, J = 8.3 Hz, 1H), 7.52 (d, J = 8.3 Hz, 1H), 7.34 (d, J = 8.0 Hz, 1H), 4.53 (d, J = 6.9 Hz, 1H), 3.77 (s, 3H), 2.70 (s, 3H), 2.37-2.21 (m, 1H), 1.06 (d, J = 6.9 Hz, 3H), 1.04 (d, J = 6.6 Hz, 3H).

Example 41(24)

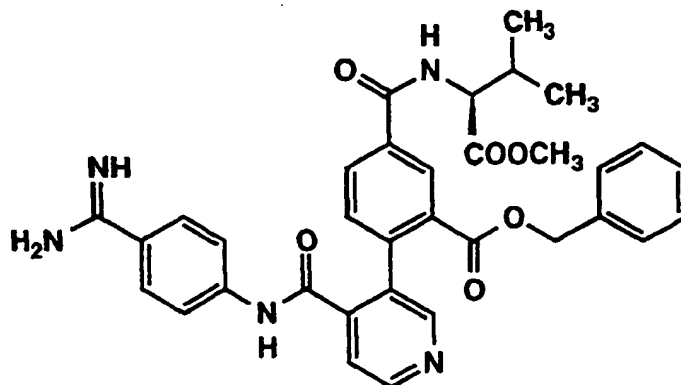
2-[4-(4-amidinophenylcarbamoyl)-3-pyridyl]-5-[(1(S)-methoxycarbonyl-2-methylpropyl)carbamoyl]benzoic acid

5 [0751]

10

15

20



25

TLC : Rf 0.39 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;
 NMR (300 MHz, CD₃OD) : δ 8.73 (d, J = 5.4 Hz, 1H), 8.51 (s, 1H), 8.42 (d, J = 1.8 Hz, 1H), 8.00 (dd, J = 8.1, 1.8 Hz, 1H), 7.71 (s, 4H), 7.70 (d, J = 5.4 Hz, 1H), 7.44 (d, J = 8.1 Hz, 1H), 4.48 (d, J = 6.9 Hz, 1H), 3.74 (s, 3H), 2.33-2.16 (m, 1H), 1.03 (d, J = 6.9 Hz, 3H), 1.01 (d, J = 6.6 Hz, 3H).

30 Example 41(25)

2'-(4-amidino-3-hydroxyphenylcarbamoyl)-4-(2-methylpropylcarbamoyl)-2-biphenylcarboxylic acid methanesulfonate

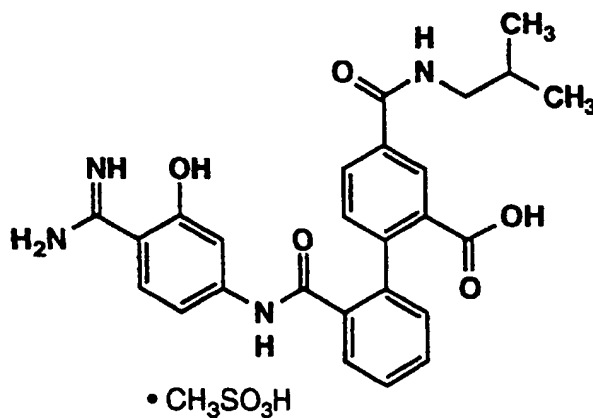
[0752]

35

40

45

50



55

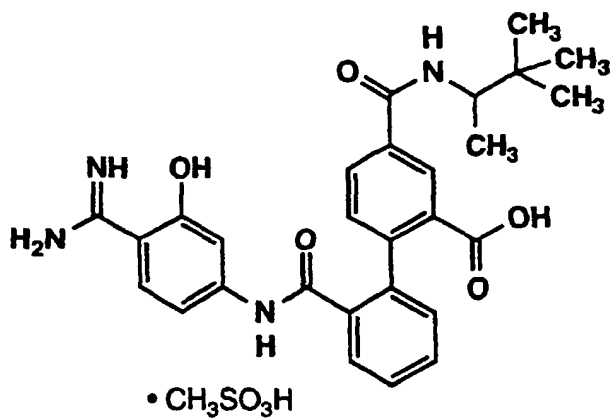
TLC : Rf 0.60 (Chloroform : Methanol : Water = 7 : 3 : 0.3) ;
 NMR (d₆-DMSO) : δ 11.15 (s, 1H), 10.39 (s, 1H), 8.79 (s, 2H), 8.66 (t, J = 6.0 Hz, 1H), 8.61 (s, 2H), 8.32 (d, J = 1.8 Hz, 1H), 7.96 (dd, J = 8.0, 1.8 Hz, 1H), 7.68 (dd, J = 8.0, 1.8 Hz, 1H), 7.59-7.52 (m, 3H), 7.48 (d, J = 8.0 Hz, 1H),

7.31 (d, J = 8.0 Hz, 1H), 7.26 (dd, J = 8.0, 1.8 Hz, 1H), 7.00 (dd, J = 8.0, 1.8 Hz, 1H), 3.10 (t, J = 6.0 Hz, 2H), 2.34 (s, 3H), 1.86 (m, 1H), 0.89 (d, J = 6.3 Hz, 6H).

Example 41(26)

2'-(4-amidino-3-hydroxyphenylcarbamoyl)-4-(1, 2, 2-trimethylpropylcarbamoyl)-2-biphenylcarboxylic acid methanesulfonate

[0753]



TLC : R_f 0.68 (Chloroform : Methanol : Water = 7 : 3 : 0.3) ;

NMR (d₆-DMSO) : δ 11.14 (br.s, 1H), 10.42 (s, 1H), 8.79 (s, 2H), 8.54 (s, 2H), 8.29 (s, 1H), 8.18 (d, J = 9.0 Hz, 1H), 7.95 (d, J = 8.0 Hz, 1H), 7.68 (d, J = 8.0 Hz, 1H), 7.58-7.52 (m, 3H), 7.48 (d, J = 8.0 Hz, 1H), 7.30 (d, J = 8.0 Hz, 1H), 7.25 (d, J = 8.0 Hz, 1H), 7.01 (d, J = 8.0 Hz, 1H), 4.00 (m, 1H), 2.31 (s, 3H), 1.09 (d, J = 7.0 Hz, 3H), 0.91 (s, 9H).

Example 41(27)

2'-(4-amidinophenylcarbamoyl)-4-(1, 3-dimethylbutylcarbamoyl)-2-biphenyl carboxylic acid methanesulfonate

5 [0754]

10

15

20

25

TLC : Rf 0.27 (Chloroform : Methanol : Water = 7 : 3 : 0.3) ;

NMR(d_6 -DMSO) : δ 12.84 (br, 1H), 10.53 (s, 1H), 9.15 (s, 2H), 8.82 (s, 2H), 8.34 (d, J = 8.4 Hz, 1H), 8.30 (d, J = 1.5 Hz, 1H), 7.96 (dd, J = 7.8, 1.5 Hz, 1H), 7.74 (dd, J = 6.9, 1.5 Hz, 1H), 7.73 (s, 4H), 7.58 (dt, J = 6.0, 1.8 Hz, 1H), 7.53 (dt, J = 7.8, 1.8 Hz, 1H), 7.32 (d, J = 8.4 Hz, 1H), 7.27 (d, J = 7.8 Hz, 1H), 4.13 (m, 1H), 2.35 (s, 3H), 1.68-1.48 (m, 2H), 1.24 (m, 1H), 1.13 (d, J = 6.3 Hz, 3H), 0.88 (d, J = 6.3 Hz, 6H)

30

Example 41(28)

35 2'-(4-amidinophenylcarbamoyl)-4-(2, 2-dimethyl-1(R)-cyclopentylcarbamoyl)-2-biphenylcarboxylic acid methanesulfonate

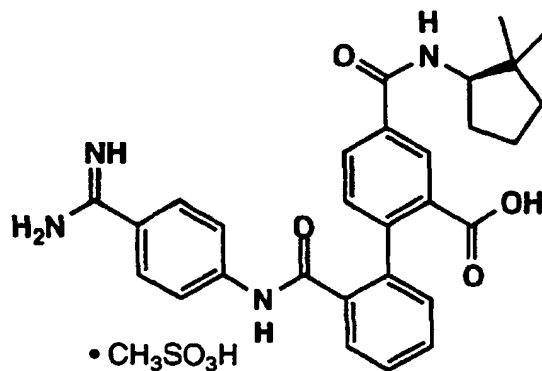
[0755]

40

45

50

55



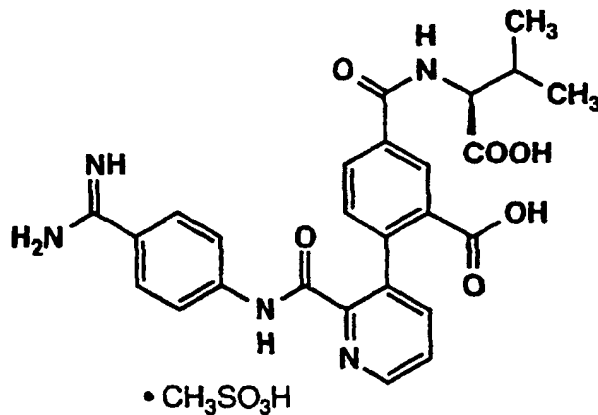
TLC : Rf 0.30 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d_6 -DMSO) : δ 13.0-12.0 (br, 1H), 10.54 (s, 1H), 9.14 (s, 2H), 8.83 (s, 2H), 8.27 (d, $J = 1.8$ Hz, 1H), 8.19 (d, $J = 8.7$ Hz, 1H), 7.95 (dd, $J = 9.7, 1.8$ Hz, 1H), 7.72 (m, 5H), 7.55 (td, $J = 7.8, 1.5$ Hz, 1H), 7.54 (td, $J = 7.8, 1.5$ Hz, 1H), 7.31 (d, $J = 9.7$ Hz, 1H), 7.26 (dd, $J = 7.8, 1.5$ Hz, 1H), 4.08 (q, $J = 8.7$ Hz, 1H), 2.33 (s, 3H), 1.90 (m, 1H), 1.74-1.40 (m, 5H), 0.98 (s, 3H), 0.87 (s, 3H)

Example 41(29)

2-[2-(4-amidinophenylcarbamoyl)-3-pyridyl]-5-[(1(S)-carboxy-2-methylpropyl) carbamoyl]benzoic acid methanesulfonate

[0756]



TLC : R_f 0.60 (Ethyl acetate : Acetic acid : Water = 3 : 1 : 0.5) ;

NMR (d_6 -DMSO) : δ 11.01 (s, 1H), 9.20 (br.s, 2H), 8.95 (br.s, 2H), 8.80-8.70 (m, 2H), 8.47 (d, $J = 1.8$ Hz, 1H), 8.10 (dd, $J = 7.8, 1.8$ Hz, 1H), 7.96 (d, $J = 8.8$ Hz, 2H), 7.77 (d, $J = 8.8$ Hz, 2H), 7.80-7.65 (m, 2H), 7.35 (d, $J = 7.8$ Hz, 1H), 6.40-4.40 (br, 2H), 4.33 (t, $J = 7.4$ Hz, 1H), 2.37 (s, 3H), 2.22 (like sextet, $J = 7.4$ Hz, 1H), 0.99 (d, $J = 7.4$ Hz, 3H), 0.98 (d, $J = 7.4$ Hz, 3H).

Example 41(30)

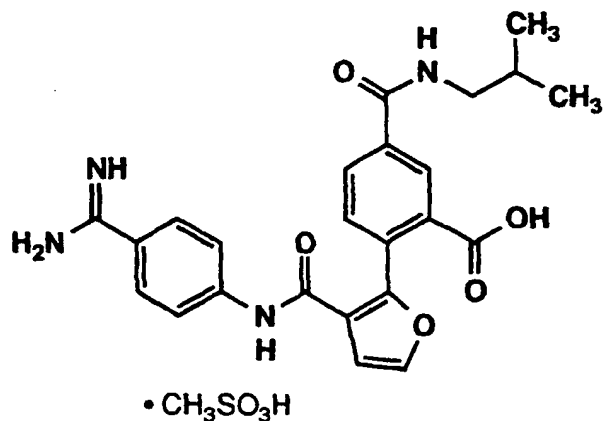
2-[3-(4-amidinophenylcarbamoyl)-2-furyl]-5-(2-methylpropylcarbamoyl)benzoic acid methanesulfonate

5 [0757]

10

15

20



25

TLC : R_f 0.39 (Chloroform : Methanol : Water = 7 : 3 : 0.3) ;

NMR (d₆-DMSO) : δ 13.0 (brs, 1H), 10.29 (s, 1H), 9.20 (brs, 2H), 8.89 (brs, 2H), 8.74 (brt, J = 6.0 Hz, 1H), 8.32 (d, J = 2.0 Hz, 1H), 8.05 (dd, J = 8.0, 2.0 Hz, 1H), 7.91 (d, J = 8.7 Hz, 2H), 7.89 (d, J = 2.0 Hz, 1H), 7.79 (d, J = 8.7 Hz, 2H), 7.69 (d, J = 8.0 Hz, 1H), 7.29 (d, J = 2.0 Hz, 1H), 3.11 (brt, J = 6.5 Hz, 2H), 2.33 (s, 3H), 1.94-1.79 (m, 1H), 0.90 (d, J = 6.5 Hz, 6H).

30

Example 41(31)

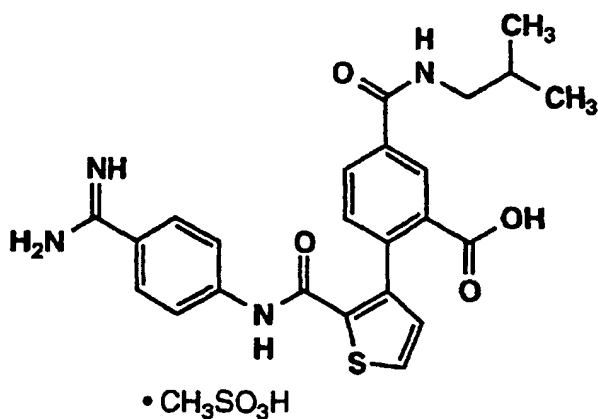
35 2-[2-(4-amidinophenylcarbamoyl)-3-thienyl]-5-(2-methylpropylcarbamoyl) benzoic acid methanesulfonate

[0758]

40

45

50



55

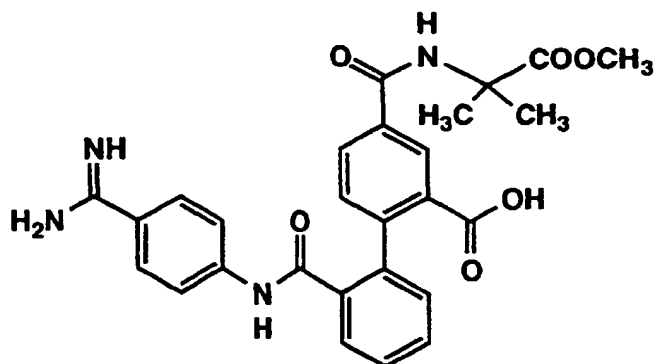
TLC : Rf 0.56 (Chloroform : Methanol : Water = 7 : 3 : 0.3) ;

NMR (d_6 -DMSO) : δ 12.9 (brs, 1H), 10.18 (s, 1H), 9.18 (brs, 2H), 8.87 (brs, 2H), 8.67 (brt, J = 6.0 Hz, 1H), 8.30 (d, J = 2.0 Hz, 1H), 8.00 (dd, J = 8.0, 2.0 Hz, 1H), 7.84 (d, J = 5.0 Hz, 1H), 7.75 (d, J = 9.3 Hz, 2H), 7.70 (d, J = 9.3 Hz, 2H), 7.41 (d, J = 8.0 Hz, 1H), 7.11 (d, J = 5.0 Hz, 1H), 3.09 (brt, J = 6.5 Hz, 2H), 2.32 (s, 3H), 1.92-1.78 (m, 1H), 0.89 (d, J = 6.5 Hz, 6H).

Example 41(32)

2'-(4-amidinophenylcarbamoyl)-4-[(1-methoxycarbonyl-1-methylethyl) carbamoyl]-2-biphenylcarboxylic acid

[0759]



TLC : Rf 0.25 (Chloroform : Methanol : Acetic acid = 20 : 2 : 1) ;

NMR (300 MHz, DMSO- d_6) : δ 12.82 (brs, 1H), 10.56 (s, 1H), 9.15 (s, 2H), 8.84 (s, 2H), 8.82 (s, 1H), 8.31 (d, J = 2.0 Hz, 1H), 7.98 (dd, J = 8.1, 2.0 Hz, 1H), 7.74 (s, 2H), 7.67 (dd, J = 6.6, 2.0 Hz, 1H), 7.59 (dt, J = 7.2, 2.0 Hz, 1H), 7.53 (dt, J = 7.2, 2.0 Hz, 1H), 7.33 (d, J = 8.1 Hz, 1H), 7.28 (dd, J = 7.8, 2.0 Hz, 1H), 3.59 (s, 3H), 2.34 (s, 3H), 1.47 (s, 6H).

Example 41(33)

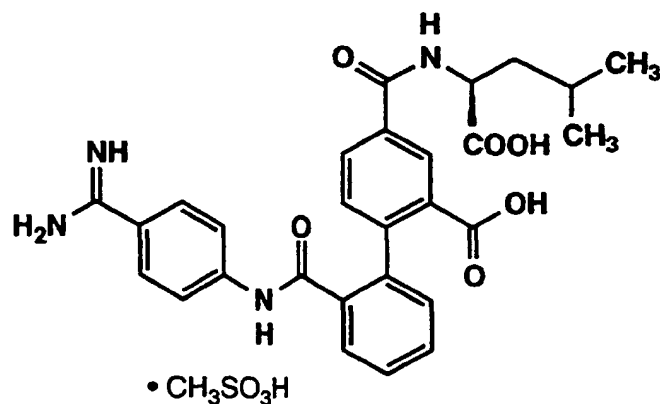
2'-[4-(4-amidinophenylcarbamoyl)-4-(1(S)-carboxy-3-methylbutylcarbamoyl)-2-biphenylcarboxylic acid methanesulfonate

5 [0760]

10

15

20



25

TLC : R_f 0.56 (Chloroform : Methanol : Water = 6 : 4 : 1) ;

NMR (d₆-DMSO) : δ 12.79 (br, 2H), 10.54 (s, 1H), 9.14 (s, 2H), 8.81 (d, J = 8.4 Hz, 1H), 8.77 (s, 2H), 8.35 (d, J = 1.8 Hz, 1H), 8.01 (dd, J = 7.8, 1.8 Hz, 1H), 7.73-7.70, (m, 5H), 7.63 (dt, J = 7.8, 1.2 Hz, 1H), 7.54 (dt, J = 6.6, 1.8 Hz, 1H), 7.35 (d, J = 7.8 Hz, 1H), 7.29 (dd, J = 6.6, 1.8 Hz, 1H), 4.45 (m, 1H), 1.82-1.55 (m, 3H), 0.92 (d, J = 6.6 Hz, 3H), 0.88 (d, J = 6.0 Hz, 3H)

30

Example 41(34)

2-[2-(4-amidinophenylcarbamoyl)-3-pyridyl]-5-(2, 2-dimethylpropylcarbamoyl) benzoic acid methanesulfonate

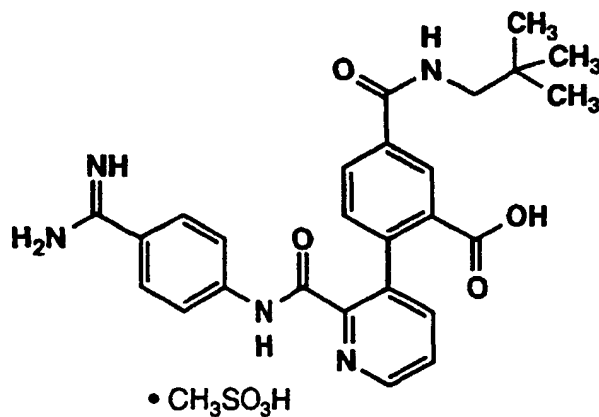
35

[0761]

40

45

50



55

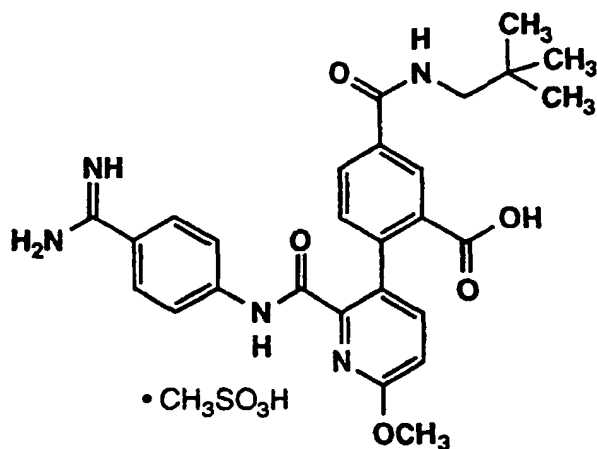
TLC : R_f 0.35 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d_6 -DMSO) : δ 11.00 (s, 1H), 9.18 (s, 2H), 8.86 (s, 2H), 8.73 (dd, J = 4.8, 2.1 Hz, 1H), 8.61 (br.t, J = 6.6 Hz, 1H), 8.43 (d, J = 1.8 Hz, 1H), 8.06 (dd, J = 7.8, 1.8 Hz, 1H), 7.95 (d, J = 9.0 Hz, 2H), 7.76 (d, J = 9.0 Hz, 2H), 7.80-7.65 (m, 2H), 7.34 (d, J = 7.8 Hz, 1H), 3.90-3.70 (br, 1H), 3.14 (d, J = 6.6 Hz, 2H), 2.34 (s, 3H), 0.92 (s, 9H).

5 Example 41(35)

2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-(2, 2-dimethylpropyl carbamoyl)benzoic acid methanesulfonate

10 [0762]



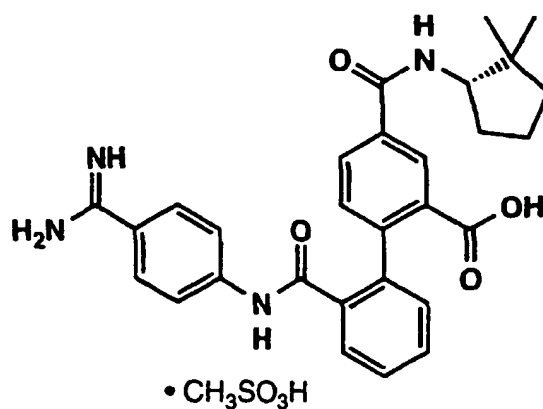
30 TLC : R_f 0.40 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d_6 -DMSO) : δ 12.9-12.5 (broad, 1H), 10.61 (s, 1H), 9.19 (brs, 2H), 8.90 (brs, 2H), 8.59 (brt, J = 6.3 Hz, 1H), 8.41 (d, J = 1.8 Hz, 1H), 8.02 (dd, J = 8.0, 1.8 Hz, 1H), 7.90 (d, J = 9.0 Hz, 2H), 7.78 (d, J = 9.0 Hz, 2H), 7.65 (d, J = 8.4 Hz, 1H), 7.30 (d, J = 8.0 Hz, 1H), 7.12 (d, J = 8.4 Hz, 1H), 4.09 (s, 3H), 3.13 (brd, J = 6.3 Hz, 2H), 2.34 (s, 3H), 0.91 (s, 9H).

Example 41(36)

2'-(4-amidinophenylcarbamoyl)-4-(2, 2-dimethyl-1(S)-cyclopentylcarbamoyl)-2-biphenylcarboxylic acid methanesulfonate

[0763]



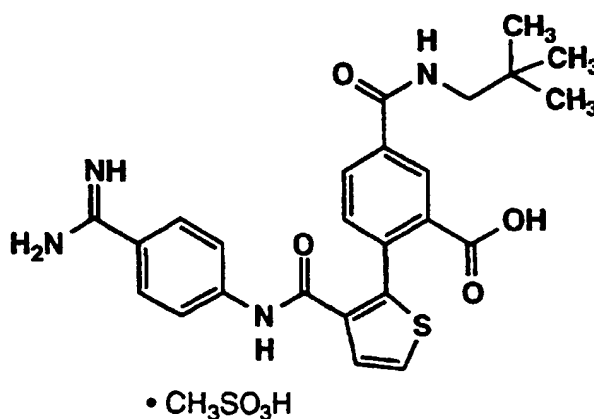
TLC : Rf 0.30 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d₆-DMSO) : δ 13.0-12.6 (br, 1H), 10.54 (s, 1H), 9.13 (s, 2H), 8.80 (s, 2H), 8.27 (d, J = 1.8 Hz, 1H), 8.18 (d, J = 8.7 Hz, 1H), 7.95 (dd, J = 8.1, 1.8 Hz, 1H), 7.72 (m, 4H), 7.69 (dd, J = 6.9, 1.2 Hz, 1H), 7.57 (td, J = 6.9, 1.2 Hz, 1H), 7.52 (td, J = 6.9, 1.2 Hz, 1H), 7.31 (d, J = 8.1 Hz, 1H), 7.26 (dd, J = 6.9, 1.2 Hz, 1H), 4.08 (q, J = 8.7 Hz, 1H), 2.31 (s, 3H), 1.90 (m, 1H), 1.80-1.40 (m, 5H), 0.97 (s, 3H), 0.87 (s, 3H).

Example 41(37)

2-[3-(4-amidinophenylcarbamoyl)-2-thienyl]-5-(2, 2-dimethylpropylcarbamoyl) benzoic acid methanesulfonate

[0764]



EP 1 078 917 A1

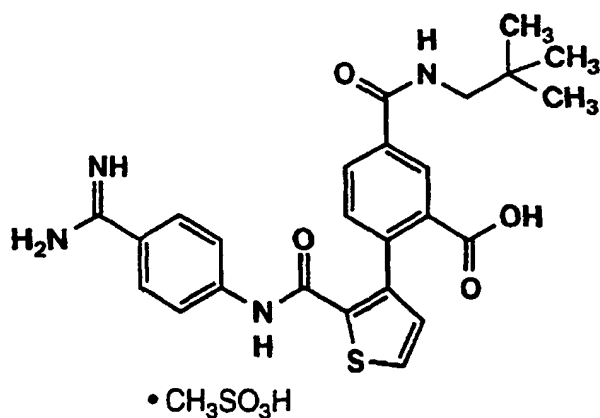
TLC : Rf 0.21 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d_6 -DMSO) : δ 13.2-12.6 (br, 1H), 10.31 (s, 1H), 9.16 (s, 2H), 8.82 (s, 2H), 8.59 (br.t, J = 6.3 Hz, 1H), 8.31 (d, J = 1.8 Hz, 1H), 8.01 (dd, J = 8.0, 1.8 Hz, 1H), 7.82 (d, J = 8.7 Hz, 2H), 7.75 (d, J = 8.7 Hz, 2H), 7.73 (d, J = 5.4 Hz, 1H), 7.64 (d, J = 5.4 Hz, 1H), 7.49 (d, J = 8.0 Hz, 1H), 3.12 (d, J = 6.3 Hz, 2H), 2.32 (s, 3H), 0.90 (s, 9H).

Example 41(38)

2-[2-(4-amidinophenylcarbamoyl)-3-thienyl]-5-(2, 2-dimethylpropylcarbamoyl) benzoic acid methanesulfonate

[0765]



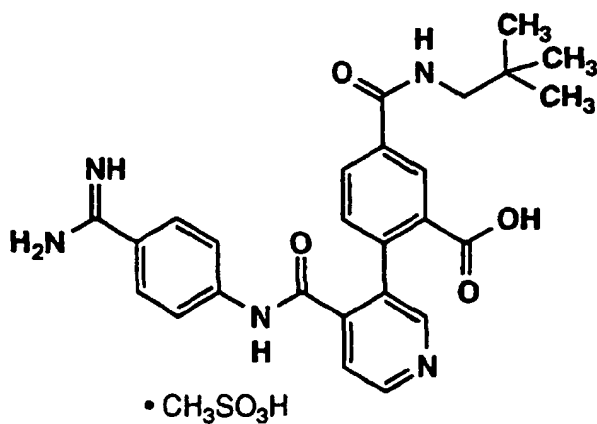
TLC : Rf 0.21 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d_6 -DMSO) : δ 13.0-12.4 (br, 1H), 10.18 (s, 1H), 9.16 (s, 2H), 8.84 (s, 2H), 8.57 (br.t, J = 6.6 Hz, 1H), 8.30 (d, J = 1.8 Hz, 1H), 8.01 (dd, J = 8.0, 1.8 Hz, 1H), 7.84 (d, J = 5.1 Hz, 1H), 7.74 (d, J = 9.0 Hz, 2H), 7.70 (d, J = 9.0 Hz, 2H), 7.42 (d, J = 8.0 Hz, 1H), 7.12 (d, J = 5.1 Hz, 1H), 3.12 (d, J = 6.6 Hz, 2H), 2.32 (s, 3H), 0.90 (s, 9H).

Example 41(39)

2-[4-(4-amidinophenylcarbamoyl)-3-pyridyl]-5-(2, 2-dimethylpropylcarbamoyl) benzoic acid methanesulfonate

[0766]



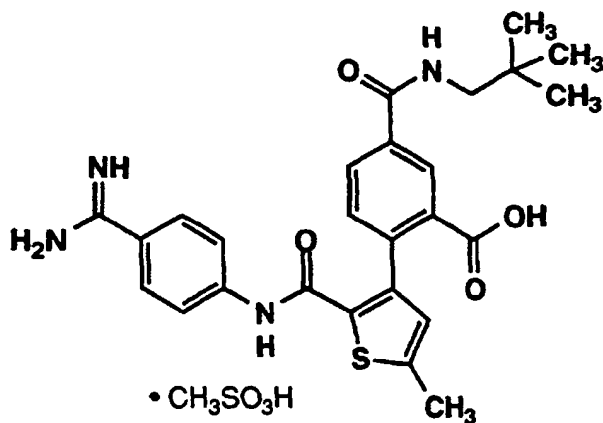
TLC : Rf 0.60 (Chloroform : Methanol : Water = 7 : 3 : 0.3) ;

NMR (d_6 -DMSO) : δ 10.96 (s, 1H), 9.21 (s, 2H), 8.93 (s, 2H), 8.86(d, J = 5.1 Hz, 1H), 8.66 (s, 1H), 8.62 (t, J = 6.2 Hz, 1H), 8.41 (d, J = 1.8 Hz, 1H), 8.06 (dd, J = 8.1, 2.1 Hz, 1H), 7.85 (d, J = 5.1 Hz, 1H), 7.76 (s, 4H), 7.46 (d, J = 8.1 Hz, 1H), 3.12 (d, J = 6.2 Hz, 1H), 2.37 (s, 3H), 0.91 (s, 9H).

Example 41(40)

2-[2-(4-amidinophenylcarbamoyl)-5-methyl-3-thienyl]-5-(2, 2-dimethylpropyl carbamoyl)benzoic acid methanesulfonate

[0767]



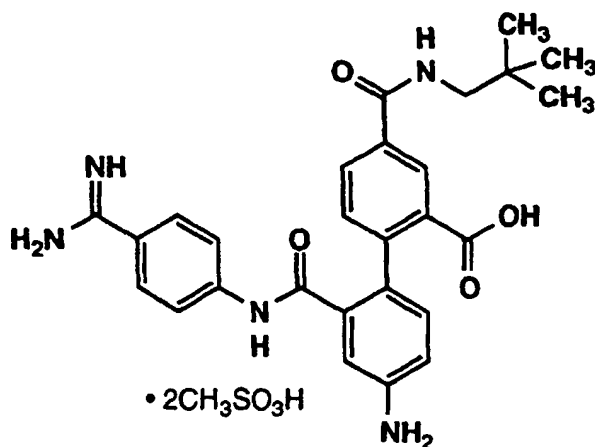
TLC : Rf 0.61 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d_6 -DMSO) : δ 12.87 (br, 1H), 9.97 (s, 1H), 9.15 (s, 2H), 8.80 (s, 2H), 8.56 (t, J = 6.6 Hz, 1H), 8.28 (d, J = 1.5 Hz, 1H), 8.00 (dd, J = 8.0, 1.5 Hz, 1H), 7.73 (d, J = 9.0 Hz, 2H), 7.67 (d, J = 9.0 Hz, 2H), 7.39 (d, J = 8.0 Hz, 1H), 6.85 (s, 1H), 3.11 (d, J = 6.6 Hz, 2H), 2.54 (s, 3H), 2.31 (s, 3H), 0.90 (s, 9H).

Example 41(41)

2'-(4-amidinophenylcarbamoyl)-4'-amino-4-(2, 2-dimethylpropylcarbamoyl)-2-biphenylcarboxylic acid dimethanesulfonate

[0768]



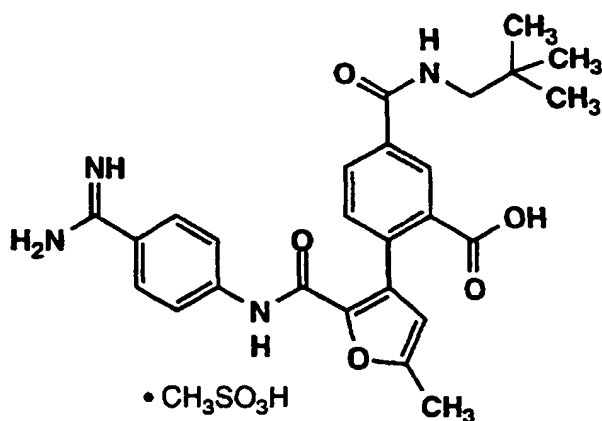
TLC : R_f 0.35 (Chloroform : Methanol : Water = 7 : 3 : 0.3) ;

NMR (d₆-DMSO) : δ 10.49 (s, 1H), 9.13 (s, 2H), 8.78 (s, 2H), 8.50 (br.t, J = 6.3 Hz, 1H), 8.24 (d, J = 1.8 Hz, 1H), 7.92 (dd, J = 8.0, 1.8 Hz, 1H), 7.71 (s, 4H), 7.29 (d, J = 8.0 Hz, 1H), 7.11-7.01 (m, 3H), 3.10 (d, J = 6.3 Hz, 2H), 2.35 (s, 6H), 0.89 (s, 9H).

Example 41(42)

2-[2-(4-amidinophenylcarbamoyl)-5-methyl-3-furyl]-5-(2, 2-dimethylpropyl carbamoyl)benzoic acid methanesulfonate

[0769]



EP 1 078 917 A1

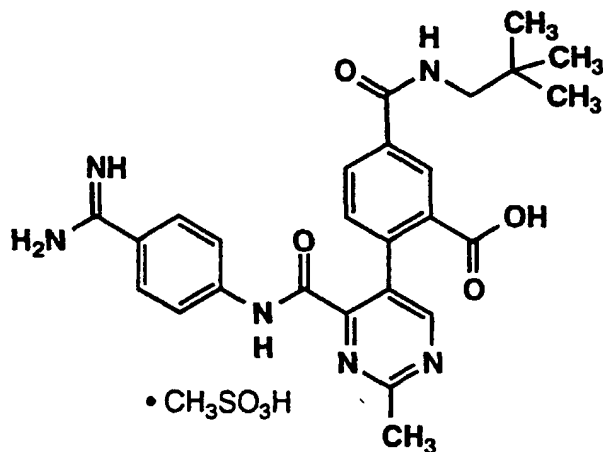
TLC : Rf 0.29 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d_6 -DMSO) : δ 13.0-12.4 (br, 1H), 10.42 (s, 1H), 9.18 (s, 2H), 8.87 (s, 2H), 8.57 (br.t, J = 6.6 Hz, 1H), 8.33 (d, J = 1.5 Hz, 1H), 8.00 (dd, J = 7.8, 1.5 Hz, 1H), 7.93 (d, J = 9.0 Hz, 2H), 7.77 (d, J = 9.0 Hz, 2H), 7.45 (d, J = 7.8 Hz, 1H), 6.43 (s, 1H), 3.13 (d, J = 6.6 Hz, 2H), 2.46 (s, 3H), 2.33 (s, 3H), 0.91 (s, 9H).

Example 41(43)

2-[4-(4-amidinophenylcarbamoyl)-2-methyl-pyrimidin-5-yl]-5-(2, 2-dimethylpropyl carbamoyl)benzoic acid methanesulfonate

[0770]



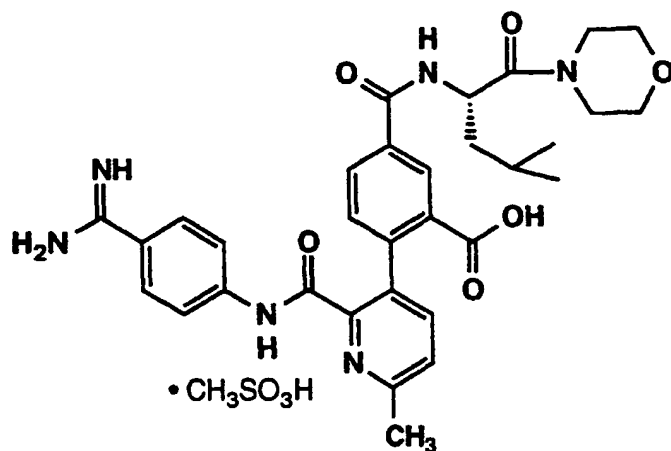
TLC : Rf 0.40 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d_6 -DMSO) : δ 11.02 (s, 1H), 9.20 (brs, 2H), 8.85 (brs, 2H), 8.73 (s, 1H), 8.62 (brt, J = 6.5 Hz, 1H), 8.46 (d, J = 1.8 Hz, 1H), 8.09 (dd, J = 8.0, 1.8 Hz, 1H), 7.91 (d, J = 9.0 Hz, 2H), 7.78 (d, J = 9.0 Hz, 2H), 7.43 (d, J = 8.0 Hz, 1H), 3.14 (d, J = 6.5 Hz, 2H), 2.83 (s, 3H), 2.30 (s, 3H), 0.91 (s, 9H).

Example 41(44)

2-[2-(4-amidinophenylcarbamoyl)-6-methyl-3-pyridyl]-5-(1(S)-morpholino carbonyl-3-methylbutylcarbamoyl)benzoic acid methanesulfonate

[0771]



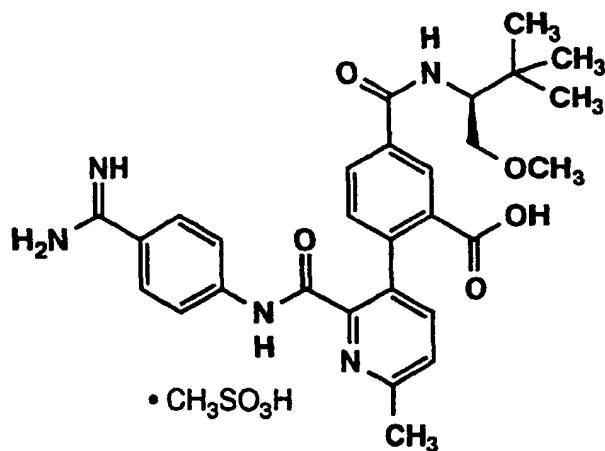
TLC : R_f 0.78 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d₆-DMSO) : δ 10.84 (s, 1H), 9.20 (s, 2H), 8.93 (s, 2H), 8.90 (d, J = 8.1 Hz, 1H), 8.46 (d, J = 1.8 Hz, 1H), 8.08 (dd, J = 8.1, 1.8 Hz, 1H), 7.83 (d, J = 9.0 Hz, 2H), 7.78 (d, J = 9.0 Hz, 2H), 7.64 (d, J = 8.1 Hz, 1H), 7.55 (d, J = 8.1 Hz, 1H), 7.31 (d, J = 8.1 Hz, 1H), 4.97 (m, 1H), 4.46 (br, 1H), 3.7-3.4 (m, 8H), 2.67 (s, 3H), 2.36 (s, 3H), 1.8-1.6 (m, 2H), 1.47 (m, 1H), 0.91 (d, J = 6.6 Hz, 3H), 0.91 (d, J = 6.6 Hz, 3H).

Example 41(45)

2-[2-(4-amidinophenylcarbamoyl)-6-methyl-3-pyridyl]-5-(1(S)-methoxymethyl-2, 2-dimethylpropylcarbamoyl)benzoic acid methanesulfonate

[0772]



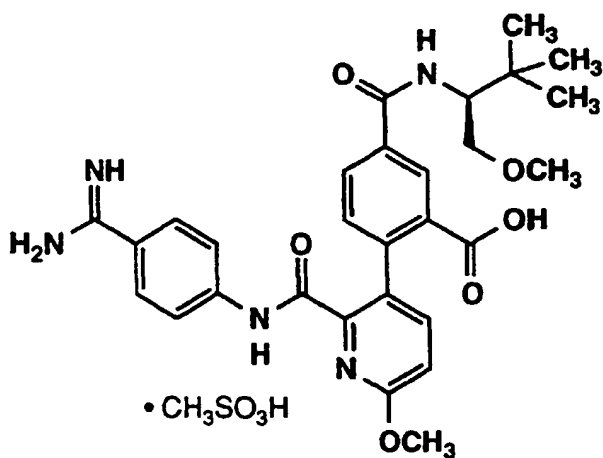
TLC : Rf 0.45 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d_6 -DMSO) : δ 10.8 (s, 1H), 9.19 (br s, 2H), 8.84 (br s, 2H), 8.41 (d, J = 1.8 Hz, 1H), 8.27 (d, J = 9.3 Hz, 1H), 8.04 (dd, J = 8.1, 1.8 Hz, 1H), 7.93 (d, J = 9.0 Hz, 2H), 7.77 (d, J = 9.0 Hz, 2H), 7.63 (d, J = 7.8 Hz, 1H), 7.56 (d, J = 7.8 Hz, 1H), 7.30 (d, J = 8.1 Hz, 1H), 4.10 (dt, J = 9.3, 3.3 Hz, 1H), 3.70-3.40 (m, 2H), 3.23 (s, 3H), 2.67 (s, 3H), 2.32 (s, 3H), 0.93 (s, 9H).

Example 41(46)

2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-(1(S)-methoxymethyl-2, 2-dimethylpropylcarbamoyl)benzoic acid methanesulfonate

[0773]



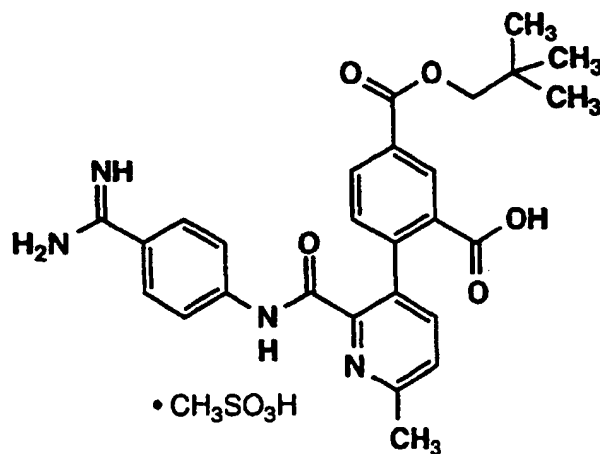
TLC : Rf 0.48 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d_6 -DMSO) : δ 10.6 (s, 1H), 9.18 (br s, 2H), 8.80 (br s, 2H), 8.40 (d, J = 2.1 Hz, 1H), 8.26 (d, J = 9.3 Hz, 1H),
 8.02 (dd, J = 8.1, 2.1 Hz, 1H), 7.90 (d, J = 9.0 Hz, 2H), 7.77 (d, J = 9.0 Hz, 2H), 7.65 (d, J = 8.1 Hz, 1H), 7.30 (d, J
 = 8.1 Hz, 1H), 7.13 (d, J = 8.1 Hz, 1H), 4.15-4.05 (m, 1H), 4.09 (s, 3H), 3.59-3.46 (m, 2H), 3.23 (s, 3H), 2.30 (s,
 3H), 0.93 (s, 9H).

Example 41(47)

2-[2-(4-amidinophenylcarbamoyl)-6-methyl-3-pyridyl]-5-(2, 2-dimethylpropyloxy carbonyl)benzoic acid methanesul-
 fonate

[0774]



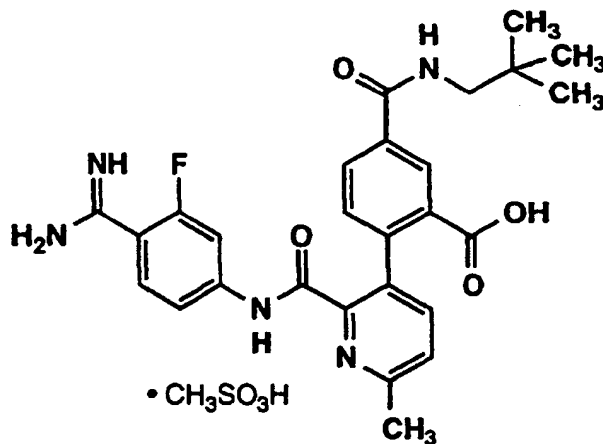
TLC : Rf 0.28 (Chloroform : Methanol : Acetic acid = 20 : 2 : 1) ;

NMR (d_6 -DMSO) : δ 10.86 (s, 1H), 9.20 (s, 2H), 8.62 (brs, 2H), 8.54 (d, J = 1.8 Hz, 1H), 8.17, (dd, J = 8.4, 1.8 Hz,
 1H), 7.94 (d, J = 8.7 Hz, 2H), 7.79 (d, J = 8.7 Hz, 2H), 7.58 (d, J = 7.8 Hz, 1H), 7.65 (d, J = 8.4 Hz, 1H), 7.39 (d, J
 = 7.8 Hz, 1H), 4.05 (s, 2H), 2.70 (s, 3H), 2.37 (s, 3H), 1.04 (s, 9H).

Example 41(48)

2-[2-(4-amidino-3-fluorophenylcarbamoyl)-6-methyl-3-pyridyl]-5-(2, 2-dimethyl propylcarbamoyl)benzoic acid methanesulfonate

[0775]



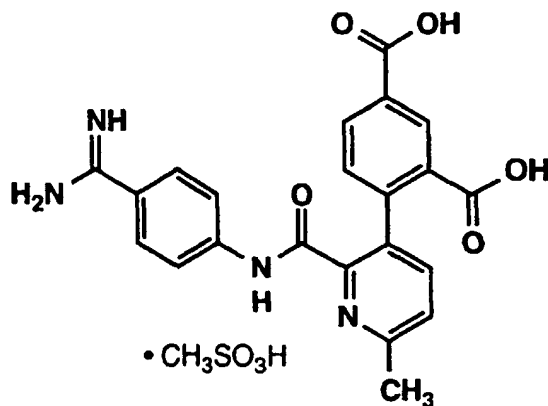
TLC : Rf 0.44 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d_6 -DMSO) : δ 11.0 (s, 1H), 9.30 (br s, 2H), 9.17 (br s, 2H^{3/5}), 9.10 (br s, 2H^{2/5}), 8.60 (t, J = 6.3 Hz, 1H), 8.41 (d, J = 2.1 Hz, 1H), 8.05 (dd, J = 7.8, 2.1 Hz, 1H), 7.85 (dd, J = 14, 2.1 Hz, 1H), 7.74 (dd, J = 9.0, 2.1 Hz, 1H), 7.65-7.60 (m, 1H), 7.64 (d, J = 7.8 Hz, 1H), 7.56 (d, J = 7.8 Hz, 1H), 7.30 (d, J = 8.1 Hz, 1H), 3.13 (d, J = 6.3 Hz, 2H), 2.67 (s, 3H), 2.36 (s, 3H^{3/5}), 2.33 (s, 3H^{2/5}), 0.91 (s, 9H).

Example 41(49)

4-[2-(4-amidinophenylcarbamoyl)-6-methyl-3-pyridyl]isophthalic acid methanesulfonate

[0776]



EP 1 078 917 A1

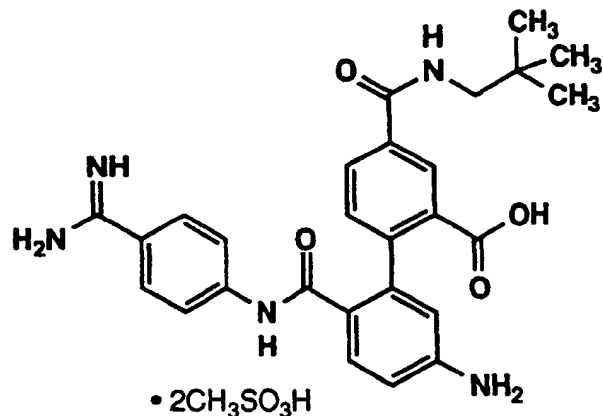
TLC : Rf 0.3 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d_6 -DMSO) : δ 10.83 (s, 1H), 9.20 (s, 2H), 8.90 (s, 2H), 8.48 (d, J = 1.8 Hz, 1H), 8.10 (dd, J = 8.1, 1.8 Hz, 1H), 7.91 (d, J = 8.7 Hz, 2H), 7.78 (d, J = 8.7 Hz, 2H), 7.64 (d, J = 7.8 Hz, 1H), 7.56 (d, J = 7.8 Hz, 1H), 7.34 (d, J = 8.1 Hz, 1H), 2.68 (s, 3H), 2.35 (s, 3H).

Example 41 (50)

2'-(4-amidinophenylcarbamoyl)-5'-amino-4-(2, 2-dimethylpropylcarbamoyl)-2-biphenylcarboxylic acid dimethanesulfonate

[0777]



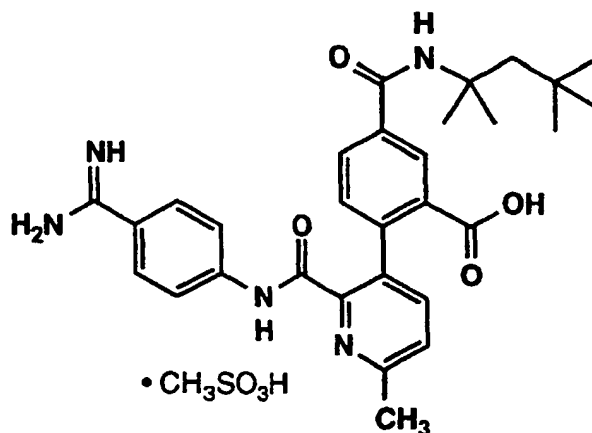
TLC : Rf 0.42 (Chloroform : Methanol : Water = 7 : 3 : 0.3) ;

NMR (d_6 -DMSO) : δ 10.24 (s, 1H), 9.10 (s, 2H), 8.80 (s, 2H), 8.51 (br.t, J = 6.0 Hz, 1H), 8.27 (d, J = 2.0 Hz, 1H), 7.94 (dd, J = 8.0, 2.0 Hz, 1H), 7.69 (s, 4H), 7.58 (d, J = 8.0 Hz, 1H), 7.24 (d, J = 8.0 Hz, 1H), 6.91 (d, J = 8.0 Hz, 1H), 6.64 (s, 1H), 3.10 (d, J = 6.0 Hz, 2H), 2.38 (s, 6H), 0.89 (s, 9H).

Example 41(51)

2-[2-(4-amidinophenylcarbamoyl)-6-methyl-3-pyridyl]-5-(1, 1, 3, 3-tetramethyl butylcarbamoyl)benzoic acid methanesulfonate

[0778]



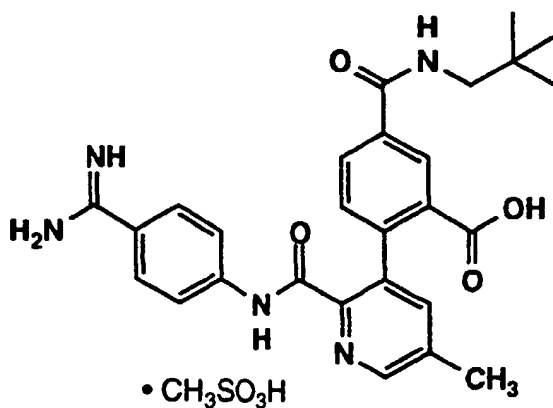
TLC : R_f 0.48 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d₆-DMSO) : δ 10.84 (s, 1H), 9.21 (brs, 2H), 8.94 (brs, 2H), 8.31 (d, J = 1.8 Hz, 1H), 7.95 (dd, J = 8.0, 1.8 Hz, 1H), 7.92 (d, J = 9.0 Hz, 2H), 7.89 (brs, 1H), 7.79 (d, J = 9.0 Hz, 2H), 7.61 (d, J = 8.0 Hz, 1H), 7.54 (d, J = 8.0 Hz, 1H), 7.26 (d, J = 8.0 Hz, 1H), 2.67 (s, 3H), 2.36 (s, 3H), 1.87 (s, 2H), 1.43 (s, 6H), 0.98 (s, 9H).

Example 41(52)

2-[2-(4-amidinophenylcarbamoyl)-5-methyl-3-pyridyl]-5-(2, 2-dimethylpropyl carbamoyl)benzoic acid methanesulfonate

[0779]



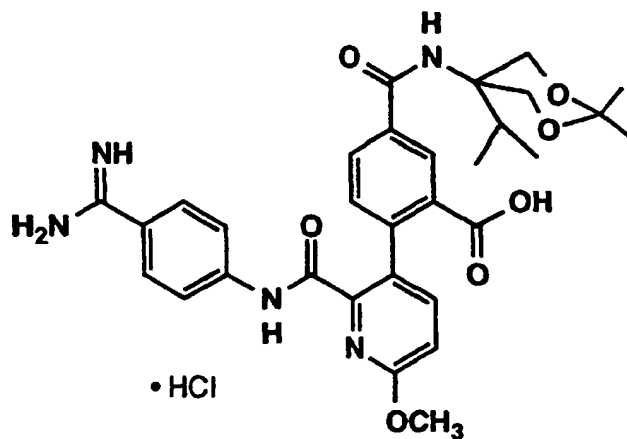
TLC : R_f 0.50 (Chloroform : Methanol : Water = 7 : 3 : 0.3) ;

NMR (d_6 -DMSO) : δ 10.93 (s, 1H), 9.18 (s, 2H), 8.88 (s, 2H), 8.60 (br.t, J = 6.2 Hz, 1H), 8.56 (d, J = 2.0 Hz, 1H), 8.43 (d, J = 2.0 Hz, 1H), 8.06 (dd, J = 8.0, 2.0 Hz, 1H), 7.95 (d, J = 9.0 Hz, 2H), 7.76 (d, J = 9.0 Hz, 2H), 7.57 (d, J = 2.0 Hz, 1H), 7.31 (d, J = 8.0 Hz, 1H), 3.14 (d, J = 6.2 Hz, 2H), 2.44 (s, 3H), 2.36 (s, 3H), 0.92 (s, 9H).

5 Example 41(53)

2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-[[5-(1-methylethyl)-2,2-dimethyldioxan-5-yl]carbamoyl]benzoic acid hydrochloride

10 [0780]



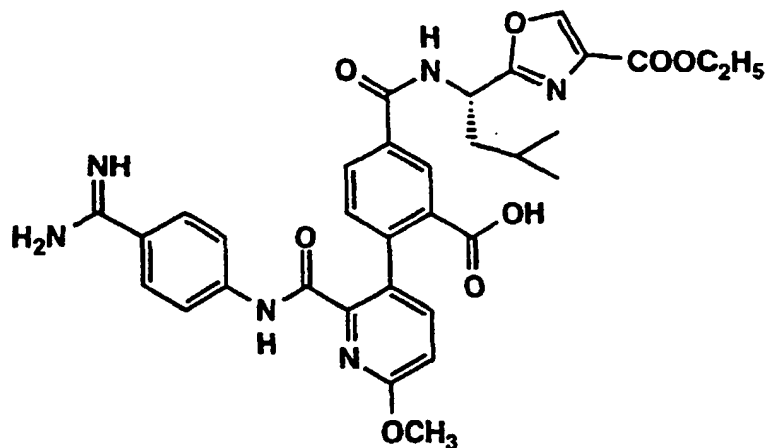
TLC : Rf 0.40 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d_6 -DMSO) : δ 12.8-12.5 (br, 1H), 9.24 (s, 2H), 9.07 (s, 2H), 8.33 (d, J = 1.8 Hz, 1H), 8.03 (s, 1H), 7.95 (dd, J = 8.1, 1.8 Hz, 1H), 7.88 (d, J = 8.7 Hz, 2H), 7.78 (d, J = 8.7 Hz, 2H), 7.62 (d, J = 8.4 Hz, 1H), 7.27 (d, J = 8.1 Hz, 1H), 7.10 (d, J = 8.4 Hz, 1H), 4.14 (d, J = 12.0 Hz, 2H), 4.08 (s, 3H), 3.93 (d, J = 11.7 Hz, 2H), 2.39 (m, 1H), 1.33 (s, 3H), 1.29 (s, 3H), 0.93 (d, J = 7.2 Hz, 6H).

Example 41 (54)

2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-[1(S)-(4-ethoxy carbonyloxazol-2-yl)-3-methylbutyl]carbamoyl]benzoic acid

[0781]



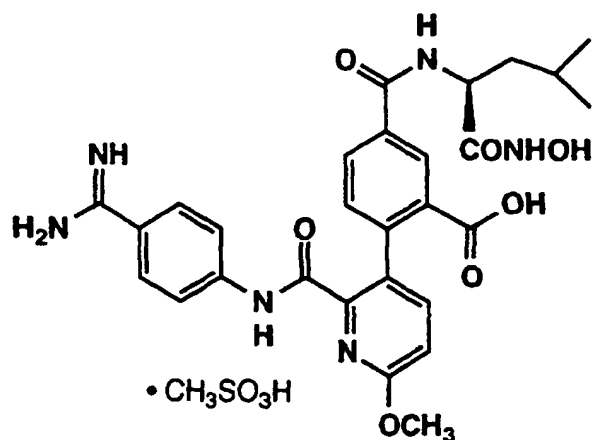
TLC : Rf 0.57 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (300 MHz, CD₃OD) : δ 8.52 (d, J = 1.8 Hz, 1H), 8.03 (dd, J = 8.0, 1.8 Hz, 1H), 7.85 (d, J = 9.0 Hz, 2H), 7.75 (d, J = 9.0 Hz, 2H), 7.59 (d, J = 8.0 Hz, 1H), 7.33 (d, J = 8.0 Hz, 1H), 7.06 (d, J = 8.0 Hz, 1H), 5.45 (dd, J = 9.3, 6.0 Hz, 1H), 4.34 (q, J = 7.2 Hz, 2H), 4.12 (s, 3H), 2.07-1.87 (m, 2H), 1.82-1.68 (m, 1H), 1.35 (t, J = 7.2 Hz, 3H), 1.03 (d, J = 6.6 Hz, 3H), 1.01 (d, J = 6.9 Hz, 3H).

Example 41(55)

2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-[(1(S)-N-hydroxy carbamoyl)-3-methylbutylcarbamoyl]benzoic acid methanesulfonate

[0782]



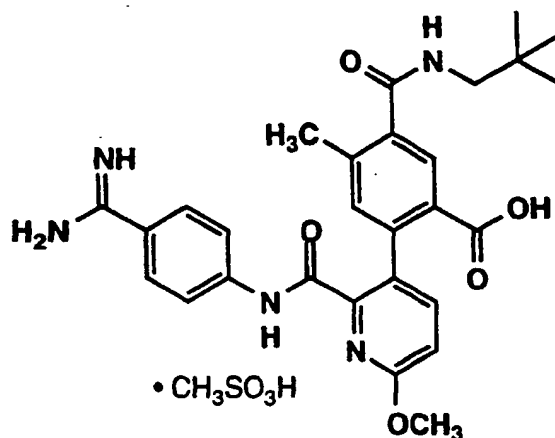
TLC : R_f 0.39 (Chloroform : Methanol : Water = 8 : 2 : 0.2) ;

NMR (d₆-DMSO) : δ 10.77 (s, 1H), 10.61 (s, 1H), 9.20 (s, 2H), 8.86 (s, 2H), 8.73 (d, J = 7.8 Hz, 1H), 8.47 (d, J = 1.8 Hz, 1H), 8.08 (dd, J = 7.8, 1.8 Hz, 1H), 7.91 (d, J = 9.0 Hz, 2H), 7.79 (d, J = 9.0 Hz, 2H), 7.65 (d, J = 8.1 Hz, 1H), 7.30 (d, J = 7.8 Hz, 1H), 7.12 (d, J = 8.1 Hz, 1H), 4.49 (m, 1H), 4.11 (s, 3H), 2.35 (s, 3H), 1.80-1.60 (m, 2H), 1.51 (m, 1H), 0.93 (d, J = 6.6 Hz, 3H), 0.89 (d, J = 6.3 Hz, 3H).

Example 41(56)

2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-(2, 2-dimethylpropyl carbamoyl)-4-methylbenzoic acid methanesulfonate

[0783]



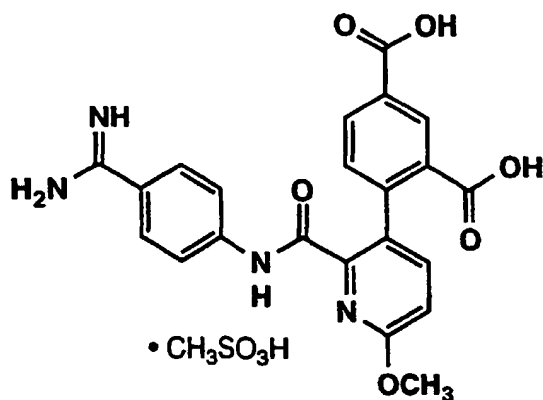
TLC : R_f 0.20 (Chloroform : Methanol : Acetic acid = 20 : 2 : 1) ;

NMR (d₆-DMSO) : δ 10.59 (s, 1H), 9.21 (s, 2H), 8.90 (s, 2H), 8.45 (br.t, J = 6.6 Hz, 1H), 7.93 (d, J = 9.0 Hz, 2H), 7.90 (s, 1H), 7.80 (d, J = 9.0 Hz, 2H), 7.59 (d, J = 8.0 Hz, 1H), 7.11 (d, J = 8.0 Hz, 1H), 7.09 (s, 1H), 4.11 (s, 3H), 3.11 (d, J = 6.6 Hz, 2H), 2.40 (s, 6H), 0.94 (s, 9H).

Example 41(57)

4-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]isophthalic acid methanesulfonate

[0784]



EP 1 078 917 A1

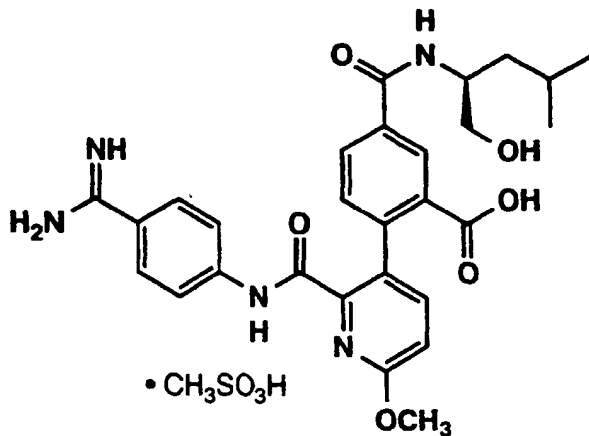
TLC : Rf 0.20 (Chloroform : Methanol : Acetic acid = 3 : 1 : 1) ;

NMR (d_6 -DMSO) : δ 10.61 (s, 1H), 9.18 (s, 2H), 8.75 (s, 2H), 8.50 (d, J = 1.8 Hz, 1H), 8.10 (dd, J = 8.0, 1.8 Hz, 1H), 7.91 (d, J = 8.7 Hz, 2H), 7.78 (d, J = 8.7 Hz, 2H), 7.67 (d, J = 8.6 Hz, 1H), 7.35 (d, J = 8.0 Hz, 1H), 7.14 (d, J = 8.6 Hz, 1H), 4.11 (s, 3H), 2.32 (s, 3H).

Example 41(58)

2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-(1(S)-hydroxymethyl-3-methylbutylcarbamoyl)-4-methylbenzoic acid methanesulfonate

[0785]



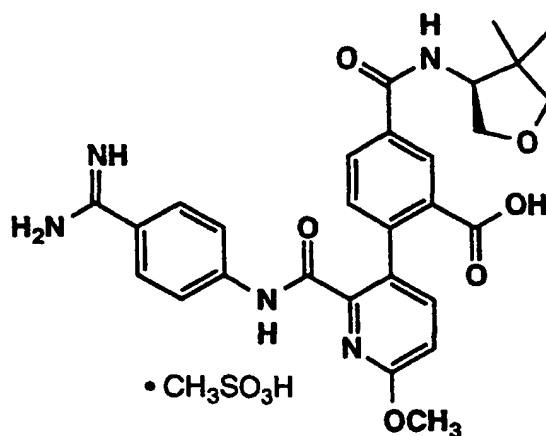
TLC : Rf 0.25 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d_6 -DMSO) : δ 12.9-12.5 (broad, 1H), 10.60 (s, 1H), 9.19 (brs, 2H), 8.86 (brs, 2H), 8.41 (d, J = 2.0 Hz, 1H), 8.25 (brd, J = 8.4 Hz, 1H), 8.02 (dd, J = 8.0, 2.0 Hz, 1H), 7.90 (d, J = 9.0 Hz, 2H), 7.78 (d, J = 9.0 Hz, 2H), 7.64 (d, J = 8.4 Hz, 1H), 7.29 (d, J = 8.0 Hz, 1H), 7.12 (d, J = 8.4 Hz, 1H), 4.15-4.05 (m, 1H), 4.09 (s, 3H), 3.47-3.32 (m, 2H), 2.32 (s, 3H), 1.72-1.56 (m, 1H), 1.55-1.30 (m, 2H), 0.90 (d, J = 6.6 Hz, 3H), 0.89 (d, J = 6.6 Hz, 3H).

Example 41 (59)

2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-[(4, 4-dimethyloxolan-3(S)-yl)carbamoyl]-4-methylbenzoic acid methanesulfonate

[0786]



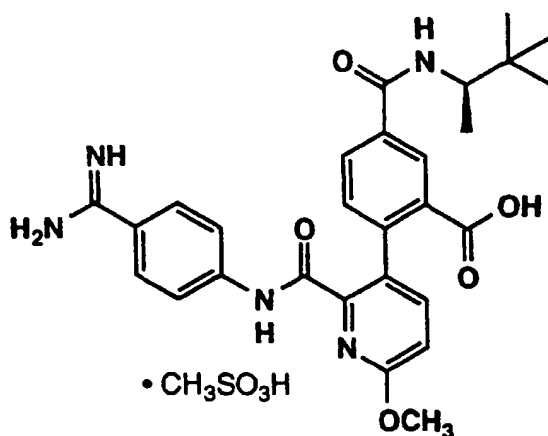
TLC : R_f 0.25 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d₆-DMSO) : δ 12.9-12.6 (broad, 1H), 10.61 (s, 1H), 9.18 (brs, 2H), 8.84 (brs, 2H), 8.55 (brd, J = 8.4 Hz, 1H), 8.42 (d, J = 2.0 Hz, 1H), 8.03 (dd, J = 8.0, 2.0 Hz, 1H), 7.89 (d, J = 9.0 Hz, 2H), 7.78 (d, J = 9.0 Hz, 2H), 7.65 (d, J = 8.4 Hz, 1H), 7.30 (d, J = 8.0 Hz, 1H), 7.12 (d, J = 8.4 Hz, 1H), 4.40-4.32 (m, 1H), 4.09 (s, 3H), 3.69 (dd, J = 9.0, 6.0 Hz, 1H), 3.53 (d, J = 5.4 Hz, 1H), 3.48 (d, J = 5.4 Hz, 1H), 2.31 (s, 3H), 1.10 (s, 3H), 0.96 (s, 3H).

Example 41 (60)

2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-(1(R), 2, 2-trimethyl propylcarbamoyl)benzoic acid methanesulfonate

[0787]



EP 1 078 917 A1

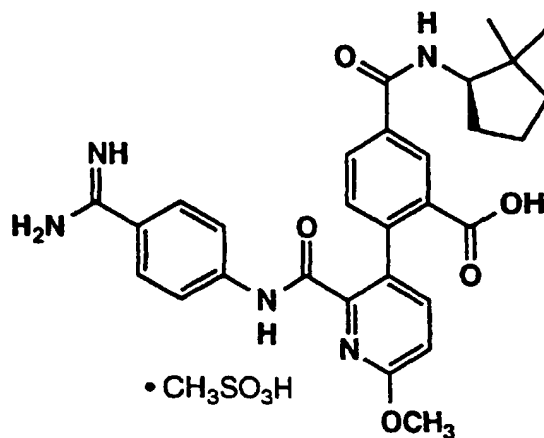
TLC : Rf 0.40 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d₆-DMSO) : δ 12.9-12.5 (broad, 1H), 10.61 (s, 1H), 9.20 (brs, 2H), 8.90 (brs, 2H), 8.37 (d, J = 1.8 Hz, 1H), 8.21 (brd, J = 9.0 Hz, 1H), 8.00 (dd, J = 8.0, 1.8 Hz, 1H), 7.90 (d, J = 9.0 Hz, 2H), 7.78 (d, J = 9.0 Hz, 2H), 7.63 (d, J = 8.4 Hz, 1H), 7.28 (d, J = 8.0 Hz, 1H), 7.12 (d, J = 8.4 Hz, 1H), 4.09 (s, 3H), 4.06-3.96 (m, 1H), 2.33 (s, 3H), 1.10 (d, J = 6.6 Hz, 3H), 0.92 (s, 9H).

Example 41(61)

2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-[(1R)-2, 2-dimethyl cyclopentyl)carbamoyl]benzoic acid
methanesulfonate

[0788]



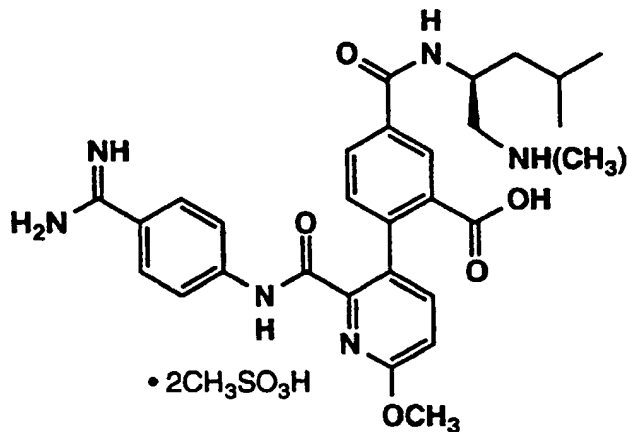
TLC : Rf 0.42 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d₆-DMSO) : δ 12.9-12.5 (broad, 1H), 10.61 (s, 1H), 9.20 (brs, 2H), 8.89 (brs, 2H), 8.38 (d, J = 1.8 Hz, 1H), 8.22 (brd, J = 8.7 Hz, 1H), 8.01 (dd, J = 8.0, 1.8 Hz, 1H), 7.90 (d, J = 9.0 Hz, 2H), 7.78 (d, J = 9.0 Hz, 2H), 7.64 (d, J = 8.4 Hz, 1H), 7.29 (d, J = 8.0 Hz, 1H), 7.12 (d, J = 8.4 Hz, 1H), 4.16-4.08 (m, 1H), 4.09 (s, 3H), 2.32 (s, 3H), 2.00-1.88 (m, 1H), 1.83-1.42 (m, 5H), 1.00 (s, 3H), 0.90 (s, 3H).

Example 41(62)

2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-[(1(S)-methylamino methyl-3-methylbutyl)carbamoyl]benzoic acid dimethanesulfonate

[0789]

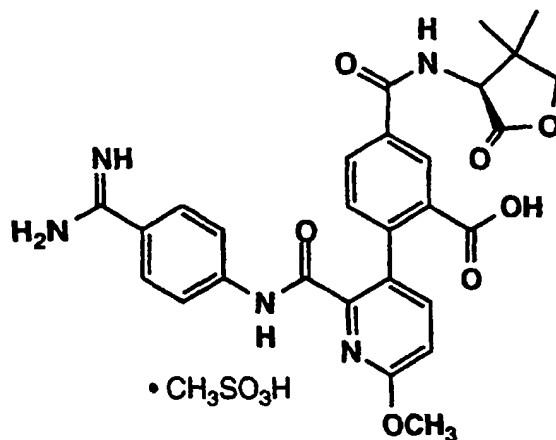
TLC : R_f 0.17 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d₆-DMSO) : δ 12.75 (br, 1H), 10.62 (s, 1H), 9.21 (s, 2H), 8.91 (s, 2H), 8.57 (d, J = 8.7 Hz, 1H), 8.60-8.40 (br, 2H), 8.48 (d, J = 1.7 Hz, 1H), 8.09 (dd, J = 8.0, 1.7 Hz, 1H), 7.91 (d, J = 9.0 Hz, 2H), 7.81 (d, J = 9.0 Hz, 2H), 7.63 (d, J = 8.7 Hz, 1H), 7.34 (d, J = 8.0 Hz, 1H), 7.14 (d, J = 8.7 Hz, 1H), 4.43 (m, 1H), 4.12 (s, 3H), 3.20-3.00 (m, 2H), 2.60 (t, J = 5.4 Hz, 3H), 2.35 (s, 6H), 1.71-1.52 (m, 2H), 1.33 (m, 1H), 0.93 (d, J = 6.3 Hz, 3H), 0.92 (d, J = 6.3 Hz, 3H).

Example 41(63)

2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-[(4, 4-dimethyl-2-oxoxolan-3(S)-yl)carbamoyl]benzoic acid
methanesulfonate

[0790]



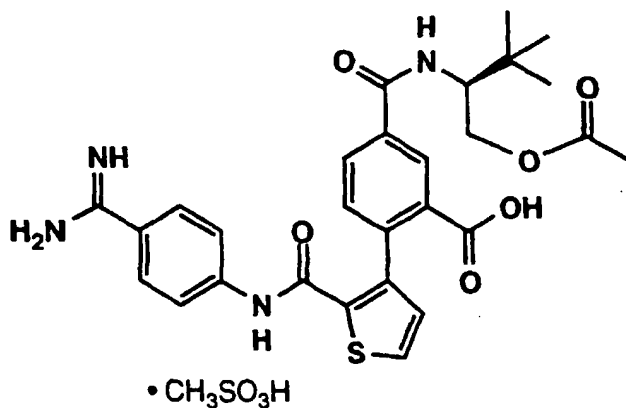
TLC : R_f 0.36 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d₆-DMSO) : δ 12.9-12.6 (broad, 1H), 10.62 (s, 1H), 9.19 (brs, 2H), 9.05 (brd, J = 9.0 Hz, 1H), 8.86 (brs, 2H), 8.50 (d, J = 1.8 Hz, 1H), 8.09 (dd, J = 8.0, 1.8 Hz, 1H), 7.90 (d, J = 9.0 Hz, 2H), 7.78 (d, J = 9.0 Hz, 2H), 7.67 (d, J = 8.4 Hz, 1H), 7.35 (d, J = 8.0 Hz, 1H), 7.13 (d, J = 8.4 Hz, 1H), 4.99 (d, J = 9.0 Hz, 1H), 4.16 (d, J = 9.0 Hz, 1H), 4.10 (s, 3H), 4.08 (d, J = 9.0 Hz, 1H), 2.32 (s, 3H), 1.15 (s, 3H), 1.02 (s, 3H).

Example 41(64)

2-[2-(4-amidinophenylcarbamoyl)-3-thienyl]-5-[(1(S)-acetyloxymethyl-2, 2-dimethylpropyl)carbamoyl]benzoic acid
methanesulfonate

[0791]



EP 1 078 917 A1

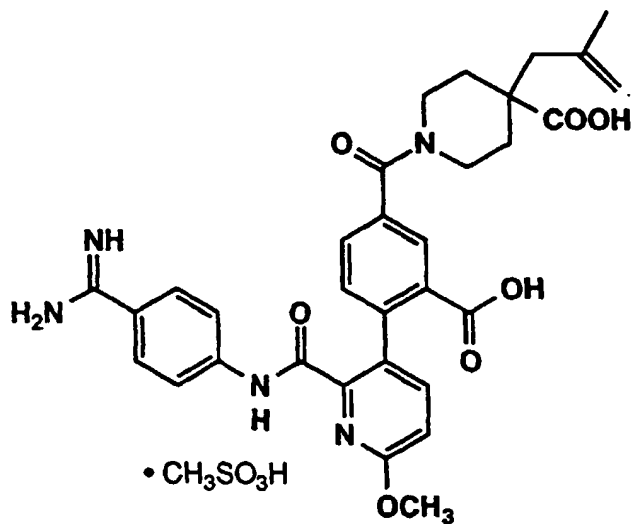
TLC : Rf 0.58 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d_6 -DMSO) : δ 12.8-12.0 (br, 1H), 10.24 (s, 1H), 9.17 (s, 2H), 8.86 (s, 2H), 8.34 (d, J = 8.4 Hz, 1H), 8.29 (d, J = 1.8 Hz, 1H), 8.00 (dd, J = 8.4, 1.8 Hz, 1H), 7.84 (d, J = 5.1 Hz, 1H), 7.74 (like s, 4H), 7.42 (d, J = 8.4 Hz, 1H), 7.11 (d, J = 5.1 Hz, 1H), 4.34 (dd, J = 10.2, 1.6 Hz, 1H), 4.13 (dd, J = 10.2, 1.6 Hz, 1H), 4.06 (t, J = 10.2 Hz, 1H), 2.33 (s, 3H), 1.93 (s, 3H), 0.94 (s, 9H).

Example 41(65)

2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-[[4-carboxy-4-(2-methyl-2-propenyl)piperidiny]carbonyl]benzoic acid methanesulfonate

[0792]



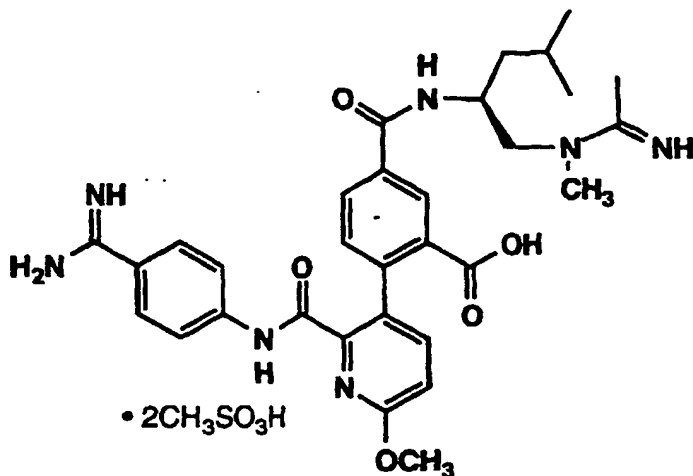
TLC : Rf 0.37 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d_6 -DMSO) : δ 10.6 (s, 1H), 9.19 (br s, 2H), 8.85 (br s, 2H), 7.91-7.88 (m, 3H), 7.78 (d, J = 8.7 Hz, 2H), 7.67 (d, J = 8.1 Hz, 1H), 7.58 (dd, J = 8.1, 1.8 Hz, 1H), 7.27 (d, J = 8.1 Hz, 1H), 7.11 (d, J = 8.1 Hz, 1H), 4.81 (s, 1H), 4.72 (s, 1H), 4.30-4.10 (m, 2H*1/2, each of isomers), 4.09 (s, 3H), 3.60-3.40 (m, 2H*1/2, each of isomers), 3.40-3.00 (m, 2H), 2.31 (s, 3H), 2.30 (s, 2H), 2.1 0-1.90 (m, 2H), 1.66 (s, 3H), 1.50-1.30 (m, 2H).

Example 41(66)

2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-[1 (S)-[N-methyl-N-(1-iminoethyl)aminomethyl]-3-methyl-butyl]benzoic acid dimethanesulfonate

[0793]



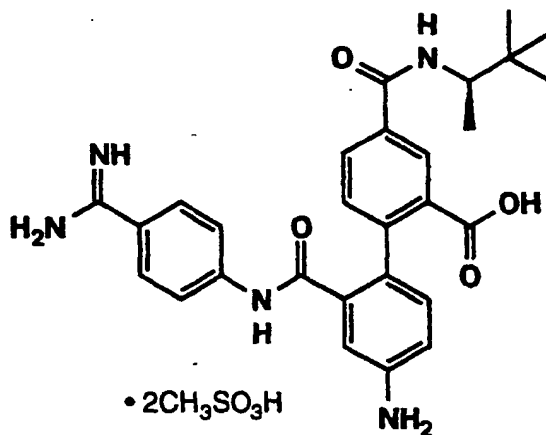
TLC : Rf 0.42 (Ethyl acetate : Acetic acid : Water = 3 : 1 : 1) ;

NMR (D₂O) : δ 8.13 (d, J = 1.8 Hz, 1H), 7.84 (d, J = 8.4 Hz, 1H), 7.72 (d, J = 8.7 Hz, 1H), 7.70 (d, J = 8.7 Hz, 2H), 7.60 (d, J = 8.7 Hz, 2H), 7.41 (d, J = 8.7 Hz, 1H), 7.13 (d, J = 8.4 Hz, 1H), 4.73 (m, 1H), 4.03 (s, 3H), 3.62 and 3.57 (d, J = 7.5 Hz, 1H), 3.21 and 3.14 (s, 3H), 2.75 (s, 6H), 2.25 and 2.18 (s, 3H), 1.76-1.54 (m, 2H), 1.39 (m, 1H), 0.92-0.85 (m, 6H).

Example 41(67)

2'-(4-amidinophenylcarbamoyl)-4'-amino-4-(1(R), 2, 2-trimethylpropyl carbamoyl)-2-biphenylcarboxylic acid dimethanesulfonate

[0794]



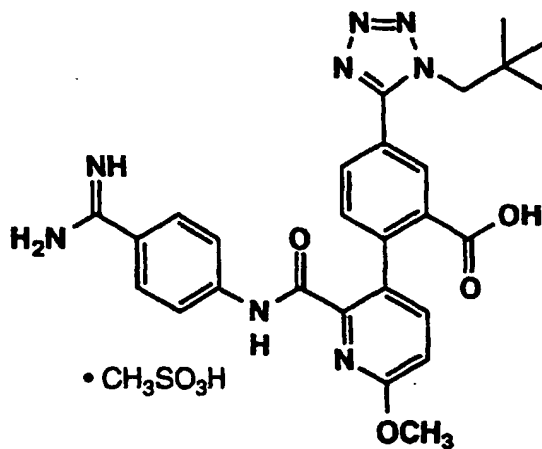
TLC : Rf 0.52 (Chloroform : Methanol : Water = 7 : 3 : 0.3) ;

NMR (d_6 -DMSO) : δ 10.55 (s, 1H), 9.14 (s, 2H), 8.85 (s, 2H), 8.24 (d, J = 2.0 Hz, 1H), 8.15 (br.d, J = 6.3 Hz, 1H), 7.93 (dd, J = 8.0, 2.0 Hz, 1H), 7.74 (d, J = 9.0 Hz, 2H), 7.70 (d, J = 9.0 Hz, 2H), 7.30 (d, J = 8.0 Hz, 1H), 7.29 (s, 1H), 7.17 (s, 2H), 3.98 (m, 1H), 2.37 (s, 6H), 1.08 (d, J = 7.0 Hz, 3H), 0.90 (s, 9H).

Example 41(68)

2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-[1-(2, 2-dimethyl propyl)tetrazol-5-yl]benzoic acid methanesulfonate

[0795]



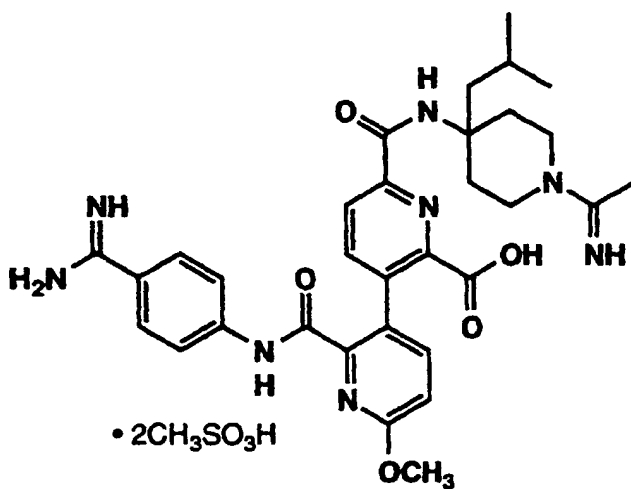
TLC : Rf 0.24 (Chloroform : Methanol : Acetic acid = 10 : 1 : 0.2) ;

NMR (d_6 -DMSO) : δ 13.2-12.3 (br, 1H), 10.62 (s, 1H), 9.19 (s, 2H), 8.88 (s, 2H), 8.27 (d, J = 1.8 Hz, 1H), 7.99 (dd, J = 7.8, 1.8 Hz, 1H), 7.90 (d, J = 9.0 Hz, 2H), 7.79 (d, J = 9.0 Hz, 2H), 7.74 (d, J = 8.4 Hz, 1H), 7.46 (d, J = 7.8 Hz, 1H), 7.15 (d, J = 8.4 Hz, 1H), 4.38 (s, 2H), 4.10 (s, 3H), 2.32 (s, 3H), 0.80 (s, 9H).

Example 41(69)

2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-[[1-(1-iminoethyl)-4-(2-methylpropyl)piperidin-4-yl]carbamoyl]benzoic acid dimethanesulfonate

[0796]



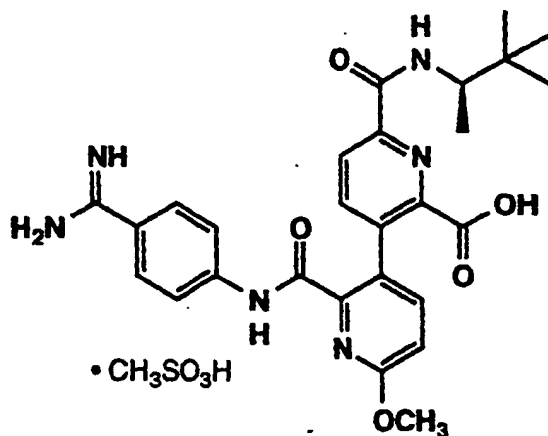
TLC : Rf 0.48 (Ethyl acetate : Acetic acid : Water = 3 : 1 : 1) ;

NMR (d_6 -DMSO) : δ 10.6 (s, 1H), 9.20 (br s, 2H), 9.08 (br s, 1H), 8.89 (br s, 2H), 8.53 (br s, 1H), 8.36 (d, J = 1.8 Hz, 1H), 8.08 (s, 1H), 8.02 (dd, J = 8.1, 1.8 Hz, 1H), 7.90 (d, J = 8.7 Hz, 2H), 7.79 (d, J = 8.7 Hz, 2H), 7.63 (d, J = 8.7 Hz, 1H), 7.30 (d, J = 8.1 Hz, 1H), 7.13 (d, J = 8.7 Hz, 1H), 4.10 (s, 3H), 3.93-3.76 (m, 2H), 3.40-3.20 (m, 2H), 2.61-2.44 (m, 2H), 2.31 (s, 6H), 2.26 (s, 3H), 1.74-1.49 (m, 5H), 0.90 (d, J = 6.0 Hz, 6H).

Example 41(70)

3-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-6-[(1(R), 2, 2-trimethyl propyl)carbamoyl]-2-pyridinecarboxylic acid methanesulfonate

[0797]



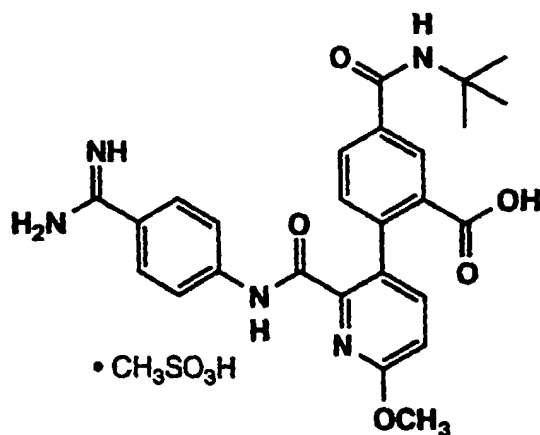
TLC : Rf 0.40 (Chloroform : Methanol : Water = 8 : 2 : 0.2) ;

NMR (d_6 -DMSO) : δ 12.95 (br.s, 1H), 10.65 (s 1H), 9.20 (s, 2H), 8.89 (s, 2H), 8.69 (d, J = 10.0 Hz, 1H), 8.26 (d, J = 8.0 Hz, 1H), 7.94 (d, J = 8.0 Hz, 1H), 7.90 (d, J = 9.0 Hz, 2H), 7.78 (d, J = 9.0 Hz, 2H), 7.74 (d, J = 8.0 Hz, 1H), 7.19 (d, J = 8.0 Hz, 1H), 4.12 (s, 3H), 4.02 (dq, J = 10.0, 7.2 Hz, 1H), 2.33 (s, 3H), 1.17 (d, J = 7.2 Hz, 3H), 0.94 (s, 9H).

Example 41(71)

2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-(t-butylcarbamoyl) benzoic acid methanesulfonate

[0798]



EP 1 078 917 A1

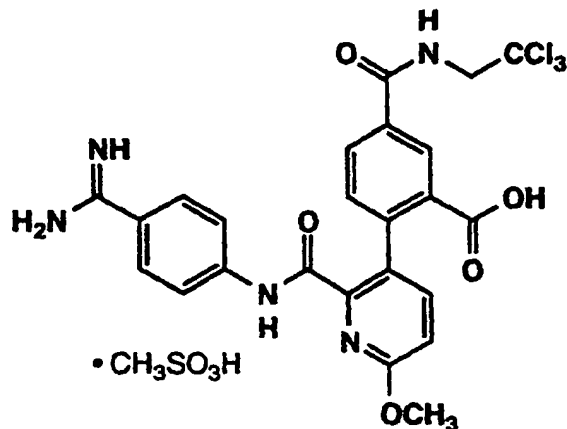
TLC : Rf 0.50 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d_6 -DMSO) : δ 10.60 (s, 1H), 9.20 (s, 2H), 8.88 (s, 2H), 8.32 (d, J = 1.8 Hz, 1H), 8.00 (s, 1H), 7.95 (dd, J = 7.8, 1.8 Hz, 1H), 7.88 (d, J = 9.3 Hz, 2H), 7.78 (d, J = 9.3 Hz, 2H), 7.62 (d, J = 8.4 Hz, 1H), 7.26 (d, J = 7.8 Hz, 1H), 7.11 (d, J = 8.4 Hz, 1H), 4.09 (s, 3H), 2.32 (s, 3H), 1.40 (s, 9H).

Example 41(72)

2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-(2, 2, 2-trichloroethyl carbamoyl)benzoic acid methanesulfonate

[0799]



TLC : Rf 0.40 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d_6 -DMSO) : δ 12.81 (s, 1H), 10.62 (s, 1H), 9.56 (t, J = 6.4 Hz, 1H), 9.20 (s, 2H), 8.86 (s, 2H), 8.49 (d, J = 1.8 Hz, 1H), 8.04 (dd, J = 8.0, 1.8 Hz, 1H), 7.90 (d, J = 9.2 Hz, 2H), 7.79 (d, J = 9.2 Hz, 2H), 7.67 (d, J = 8.6 Hz, 1H), 7.35 (d, J = 8.0 Hz, 1H), 7.13 (d, J = 8.6 Hz, 1H), 4.42 (d, J = 6.0 Hz, 2H), 4.10 (s, 3H), 2.31 (s, 3H).

Example 41(73)

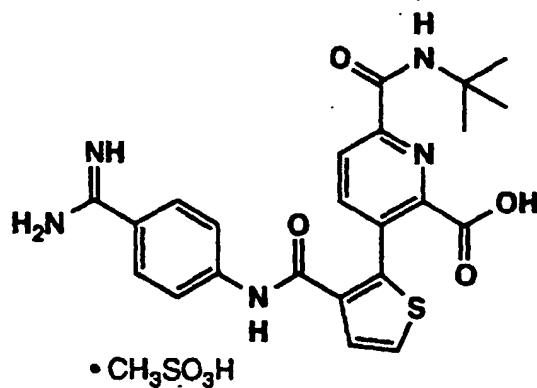
2-[3-(4-amidinophenylcarbamoyl)-2-thienyl]-6-(t-butylcarbamoyl)-2-pyridine carboxylic acid methanesulfonate

5 [0800]

10

15

20



25

TLC : R_f 0.15 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d₆-DMSO) : δ 13.05 (br.s, 1H), 10.41 (s 1H), 9.17 (s, 2H), 8.82 (s, 2H), 8.31 (s, 1H), 8.19 (d, J = 8.0 Hz, 1H), 8.07 (d, J = 8.0 Hz, 1H), 7.84 (d, J = 9.0 Hz, 2H), 7.82 (d, J = 5.4 Hz, 1H), 7.75 (d, J = 9.0 Hz, 2H), 7.73 (d, J = 5.4 Hz, 1H), 2.31 (s, 3H), 1.44 (s, 9H).

30 Example 41(74)

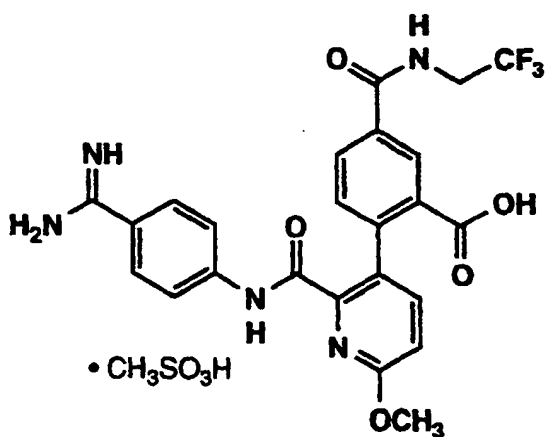
2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-(2, 2, 2-trifluoroethyl carbamoyl)benzoic acid methanesulfonate

35 [0801]

40

45

50



55

TLC : R_f 0.30 (Chloroform : Methanol : Water = 8 : 2 : 0.2) ;

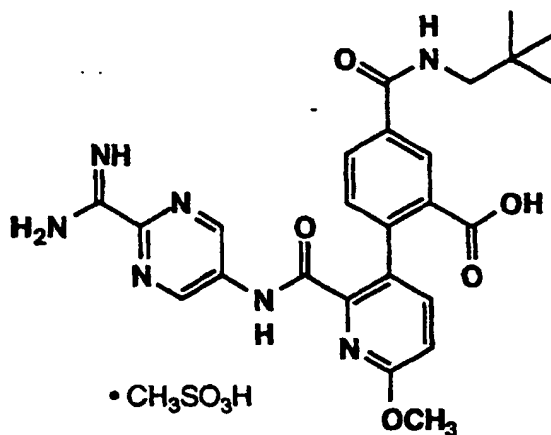
EP 1 078 917 A1

NMR (d_6 -DMSO) : δ 12.79 (brs, 1H), 10.62 (s, 1H), 9.34 (t, $J = 6.3$ Hz, 1H), 9.19 (s, 2H), 8.81 (s, 2H), 8.48 (d, $J = 1.8$ Hz, 1H), 8.08 (dd, $J = 7.8, 1.8$ Hz, 1H), 7.91 (d, $J = 8.7$ Hz, 2H), 7.78 (d, $J = 8.7$ Hz, 2H), 7.67 (d, $J = 8.4$ Hz, 1H), 7.36 (d, $J = 7.8$ Hz, 1H), 7.14 (d, $J = 8.4$ Hz, 1H), 4.22-4.10 (m, 2H), 4.11 (s, 3H), 2.32 (s, 3H).

5 Example 41 (75)

2-[2-[(2-amidinopyrimidin-5-yl)carbamoyl]-6-methoxy-3-pyridyl]-5-(2, 2-dimethyl propylcarbamoyl)benzoic acid methanesulfonate

10 [0802]



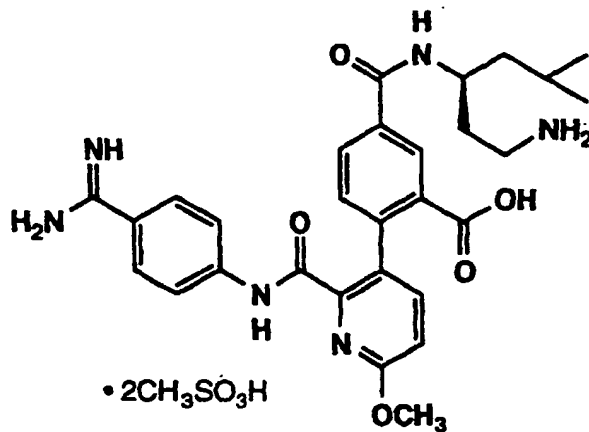
TLC : Rf 0.38 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d_6 -DMSO) : δ 13.0-12.6 (br, 1H), 11.05 (s, 1H), 9.59 (s, 2H), 9.35 (s, 2H), 9.29 (s, 2H), 8.59 (t, $J = 6.0$ Hz, 1H), 8.41 (d, $J = 1.5$ Hz, 1H), 8.04 (dd, $J = 8.0, 1.5$ Hz, 1H), 7.69 (d, $J = 8.7$ Hz, 1H), 7.34 (d, $J = 8.0$ Hz, 1H), 7.18 (d, $J = 8.7$ Hz, 1H), 4.11 (s, 3H), 3.13 (d, $J = 6.0$ Hz, 2H), 2.29 (s, 3H), 0.91 (s, 9H).

Example 41(76)

2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-[[1(S)-(2-aminoethyl)-3-methylbutyl]carbamoyl]benzoic acid dimethanesulfonate

[0803]



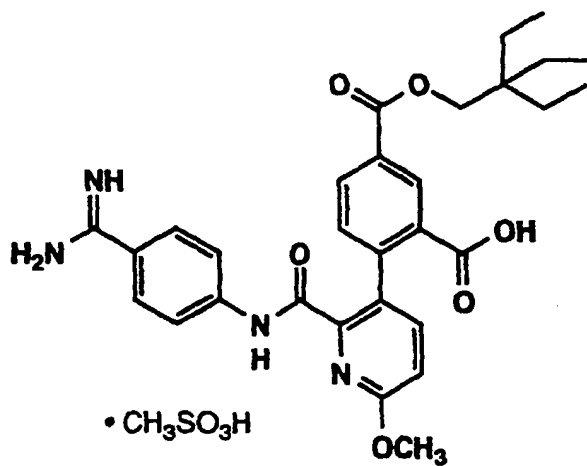
TLC : R_f 0.17 (Chloroform : Methanol : Water = 7 : 3 : 0.3) ;

NMR (d₆-DMSO) : δ 12.80 (br.s, 1H), 10.62 (s, 1H), 9.19 (s, 2H), 8.90 (s, 2H), 8.51 (d, J = 9.0 Hz, 1H), 8.42 (d, J = 2.0 Hz, 1H), 8.04 (dd, J = 8.0, 2.0 Hz, 1H), 7.90 (d, J = 9.0 Hz, 2H), 7.79 (d, J = 9.0 Hz, 2H), 7.69 (br.s, 3H), 7.64 (d, J = 8.4 Hz, 1H), 7.32 (d, J = 8.0 Hz, 1H), 7.13 (d, J = 8.4 Hz, 1H), 4.15 (m, 1H), 4.10 (s, 3H), 2.90-2.78 (m, 2H), 2.34 (s, 6H), 1.83-1.60 (m, 4H), 1.27 (m, 1H), 0.90 (d, J = 6.8 Hz, 3H), 0.88 (d, J = 6.8 Hz, 3H).

Example 41(77)

2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-(2, 2-diethylbutyloxy) carbamoyl]benzoic acid methanesulfonate

[0804]



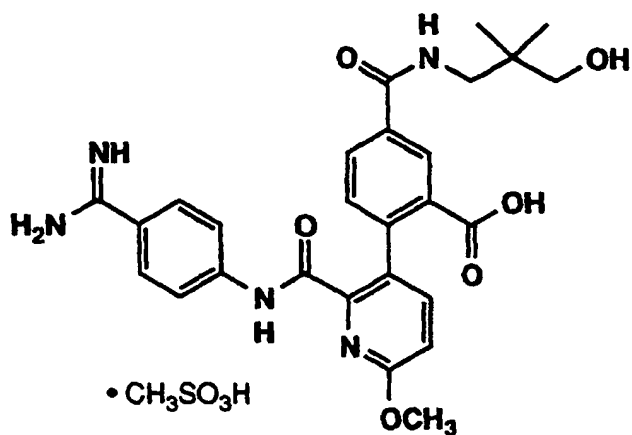
TLC : Rf 0.80 (Chloroform : Methanol : Water = 7 : 3 : 0.3) ;

NMR (d_6 -DMSO) : δ 12.86 (s, 1H), 10.63 (s, 1H), 9.20 (s, 2H), 8.86 (s, 2H), 8.50 (d, J = 1.5 Hz, 1H), 8.11 (dd, J = 8.1, 1.5 Hz, 1H), 7.91 (d, J = 9.0 Hz, 2H), 7.80 (d, J = 9.0 Hz, 2H), 7.68 (d, J = 8.7 Hz, 1H), 7.40 (d, J = 8.1 Hz, 1H), 7.15 (d, J = 8.7 Hz, 1H), 4.12 (s, 3H), 4.10 (s, 2H), 2.33 (s, 3H), 1.36 (q, J = 7.5 Hz, 6H), 0.82 (t, J = 7.5 Hz, 9H).

Example 41(78)

2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-[(2, 2-dimethyl-3-hydroxypropyl)carbamoyl]benzoic acid methanesulfonate

[0805]



TLC : Rf 0.10 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d_6 -DMSO) : δ 10.6 (s, 1H), 9.19 (br s, 2H), 8.82 (br s, 2H), 8.62 (t, J = 5.8 Hz, 1H), 8.40 (d, J = 1.8 Hz, 1H), 8.02 (dd, J = 8.2, 1.8 Hz, 1H), 7.90 (d, J = 9.2 Hz, 2H), 7.78 (d, J = 9.2 Hz, 2H), 7.66 (d, J = 8.4 Hz, 1H), 7.31 (d, J = 8.2 Hz, 1H), 7.13 (d, J = 8.4 Hz, 1H), 4.10 (s, 3H), 3.19 (d, J = 6.2 Hz, 2H), 3.15 (s, 2H), 2.31 (s, 3H), 0.85 (s, 6H).

Example 41(79)

2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-[(2, 2-diethylbutyl) carbamoyl]benzoic acid methanesulfonate

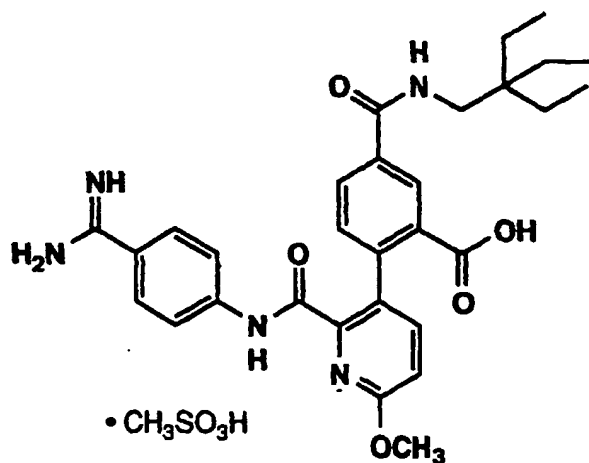
5 [0806]

10

15

20

25



TLC : R_f 0.31 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;
 NMR (d₆-DMSO) : δ 10.62 (s, 1H), 9.21 (s, 2H), 8.89 (s, 2H), 8.36 (d, J = 1.8 Hz, 1H), 8.24 (t, J = 6.6 Hz, 1H), 7.99 (dd, J = 8.4, 1.8 Hz, 1H), 7.91 (d, J = 9.0 Hz, 2H), 7.80 (d, J = 9.0 Hz, 2H), 7.65 (d, J = 8.4 Hz, 1H), 7.30 (d, J = 8.4 Hz, 1H), 7.13 (d, J = 8.4 Hz, 1H), 4.11 (s, 3H), 3.18 (d, J = 6.6 Hz, 2H), 2.34 (s, 3H), 1.24 (q, J = 7.5 Hz, 6H), 0.81 (t, J = 7.5 Hz, 9H).

35 Example 41(80)

35

2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-[(1-hydroxymethyl) cyclobutylmethyl]carbamoyl]benzoic acid methanesulfonate

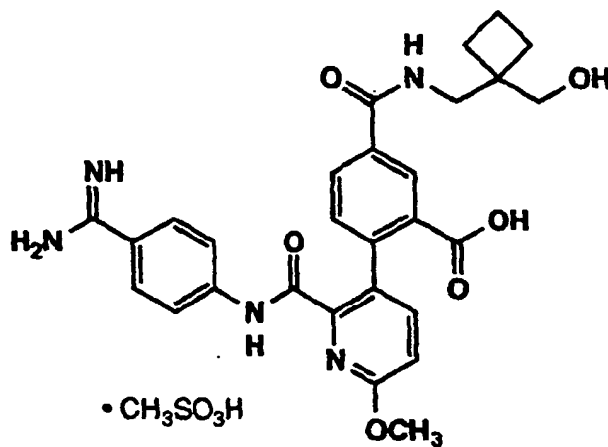
40 [0807]

40

45

50

55



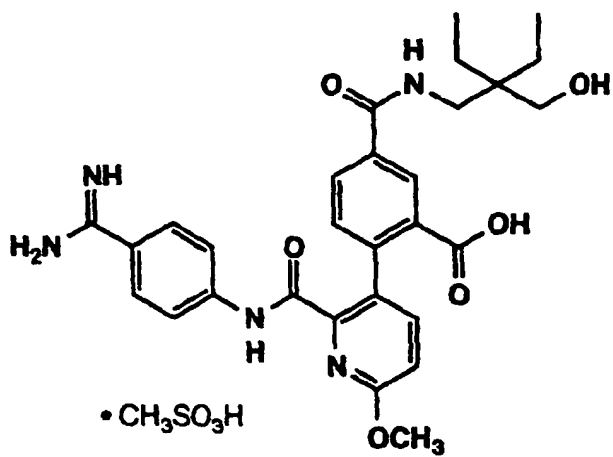
TLC : Rf 0.16 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d_6 -DMSO) : δ 10.6 (s, 1H), 9.17 (br s, 2H), 8.77 (br s, 2H), 8.66 (t, J = 6.0 Hz, 1H), 8.41 (d, J = 2.1 Hz, 1H),
 8.02 (dd, J = 7.8, 2.1 Hz, 1H), 7.90 (d, J = 8.7 Hz, 2H), 7.77 (d, J = 8.7 Hz, 2H), 7.65 (d, J = 8.1 Hz, 1H), 7.31 (d, J
 = 7.8 Hz, 1H), 7.12 (d, J = 8.1 Hz, 1H), 4.09 (s, 3H), 3.41-3.36 (m, 4H), 2.29 (s, 3H), 1.90-1.70 (m, 6H).

Example 41(81)

2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-[(2-ethyl-2-hydroxy methylbutyl)carbamoyl]benzoic acid
 methanesulfonate

[0808]



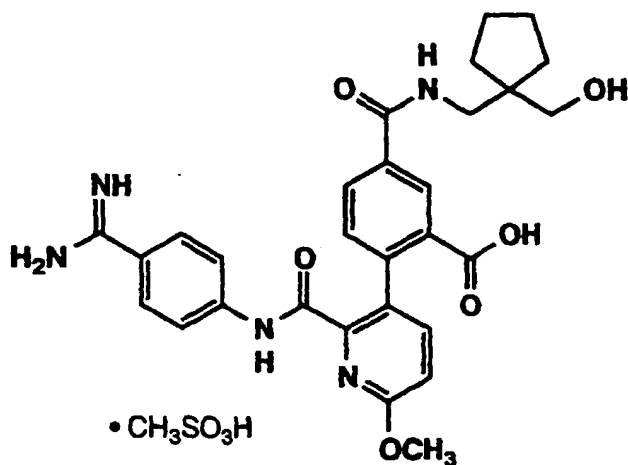
TLC : Rf 0.24 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d_6 -DMSO) : δ 10.6 (s, 1H), 9.18 (br s, 2H), 8.80 (br s, 2H), 8.49 (t, J = 6.0 Hz, 1H), 8.38 (d, J = 2.1 Hz, 1H),
 8.00 (dd, J = 8.1, 2.1 Hz, 1H), 7.90 (d, J = 8.7 Hz, 2H), 7.77 (d, J = 8.7 Hz, 2H), 7.65 (d, J = 8.4 Hz, 1H), 7.31 (d, J
 = 8.1 Hz, 1H), 7.13 (d, J = 8.4 Hz, 1H), 4.10 (s, 3H), 3.20-3.18 (m, 4H), 2.30 (s, 3H), 1.22 (septet, J = 6.6 Hz, 4H),
 0.81 (t, J = 6.6 Hz, 6H).

Example 41(82)

2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-[[[(1-hydroxymethyl) cyclopentylmethyl)carbamoyl]benzoic
acid methanesulfonate

[0809]



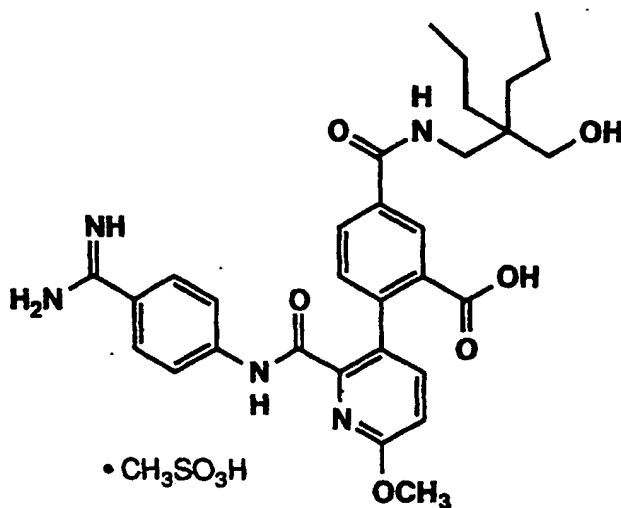
TLC : R_f 0.20 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (300 MHz, d₆-DMSO) : δ 10.6 (s, 1H), 9.19 (br s, 2H), 8.84 (br s, 2H), 8.67 (t, J = 6.3 Hz, 1H), 8.40 (d, J = 1.5 Hz, 1H), 8.02 (dd, J = 7.8, 1.5 Hz, 1H), 7.90 (d, J = 9.0 Hz, 2H), 7.78 (d, J = 9.0 Hz, 2H), 7.66 (d, J = 8.4 Hz, 1H), 7.31 (d, J = 7.8 Hz, 1H), 7.12 (d, J = 8.4 Hz, 1H), 4.10 (s, 3H), 3.36-3.22 (m, 4H), 2.30 (s, 3H), 1.57-1.38 (m, 8H).

Example 41(83)

2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-[(2-propyl-2-hydroxy methylpentyl)carbamoyl]benzoic acid
methanesulfonate

[0810]



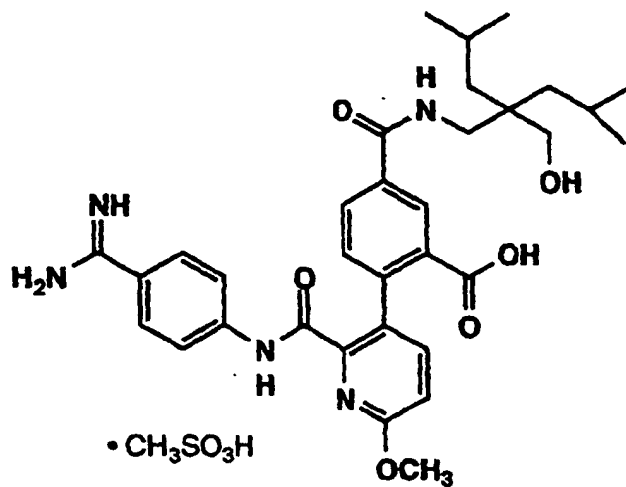
TLC : R_f 0.50 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (300 MHz, d₆-DMSO) : δ 12.8-12.3 (brd, 1H), 10.61 (s, 1H), 9.19 (s, 2H), 8.83 (s, 2H), 8.50 (t, J = 5.7 Hz, 1H), 8.37 (d, J = 1.8 Hz, 1H), 8.00 (dd, J = 8.1, 1.8 Hz, 1H), 7.90 (d, J = 8.7 Hz, 2H), 7.71 (d, J = 8.7 Hz, 2H), 7.65 (d, J = 8.7 Hz, 1H), 7.31 (d, J = 8.1 Hz, 1H), 7.12 (d, J = 8.7 Hz, 1H), 4.09 (s, 3H), 3.21-3.18 (m, 4H), 2.31 (s, 3H), 1.18-1.02 (m, 8H), 0.86 (t, J = 6.6 Hz, 6H).

Example 41(84)

2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-[(2-(2-methylpropyl)-2-hydroxymethyl-4-methylpentyl)carbamoyl]benzoic acid methanesulfonate

[0811]



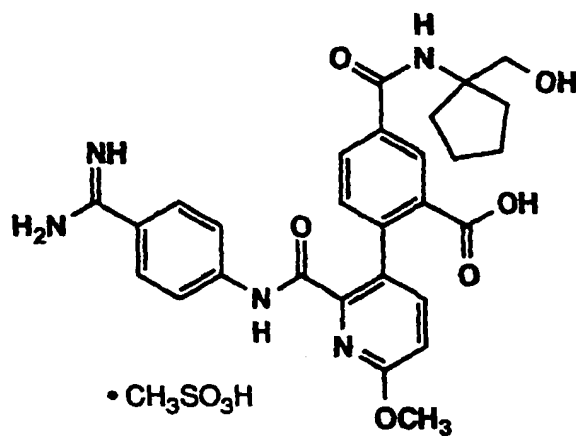
TLC : R_f 0.23 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (300 MHz, DMSO-d₆) : δ 12.74 (br, 1H), 10.62 (s, 1H), 9.19 (s, 2H), 8.12 (s, 2H), 8.42 (m, 1H), 8.37 (d, J = 1.8 Hz, 1H), 7.97 (dd, J = 8.1, 1.8 Hz, 1H), 7.91 (d, J = 9.0 Hz, 2H), 7.79 (d, J = 9.0 Hz, 2H), 7.66 (d, J = 8.4 Hz, 1H), 7.33 (d, J = 8.1 Hz, 1H), 7.13 (d, J = 8.4 Hz, 1H), 4.77 (br, 1H), 4.11 (s, 3H), 2.32 (s, 3H), 1.82-1.70 (m, 2H), 1.40-1.20 (m, 4H), 0.92 (d, J = 6.9 Hz, 6H).

Example 41(85)

2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-[(1-hydroxymethyl cyclopentyl)carbamoyl]benzoic acid methanesulfonate

[0812]



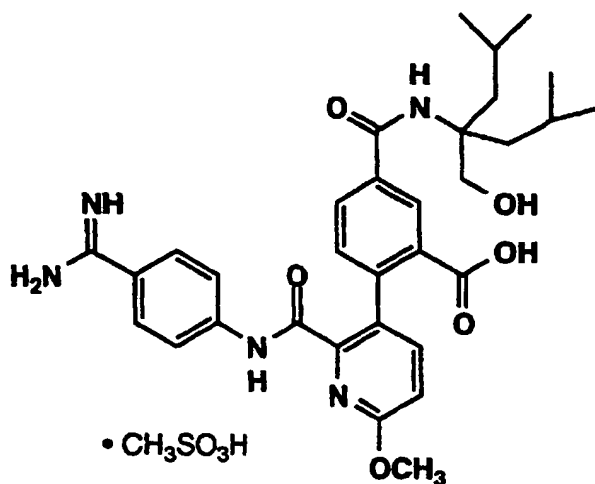
TLC : R_f 0.23 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (300 MHz, DMSO-d₆) : δ 10.61 (s, 1H), 9.20 (s, 2H), 8.87 (s, 2H), 8.36 (d, J = 1.8 Hz, 1H), 7.99 (dd, J = 8.4, 1.8 Hz, 1H), 7.98 (s, 1H), 7.91 (d, J = 9.0 Hz, 2H), 7.79 (d, J = 9.0 Hz, 2H), 7.64 (d, J = 8.4 Hz, 1H), 7.27 (d, J = 8.4 Hz, 1H), 7.13 (d, J = 8.4 Hz, 1H), 4.10 (s, 3H), 3.61 (s, 2H), 2.33 (s, 3H), 2.09-2.00 (m, 2H), 1.80-1.62 (m, 4H), 1.62-1.54 (m, 2H).

Example 41(86)

2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-[(1-(2-methylpropyl)-1-hydroxymethyl-3-methylbutyl)carbamoyl]benzoic acid methanesulfonate

[0813]



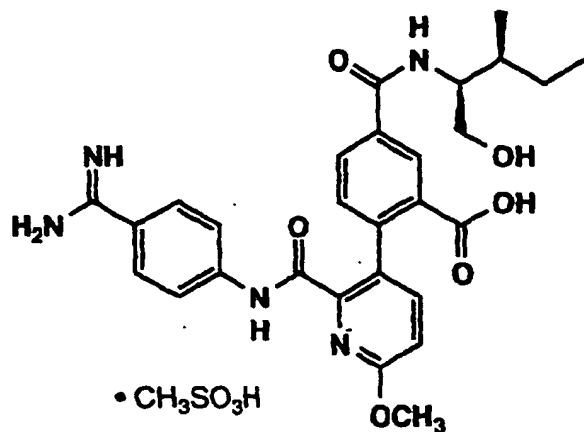
TLC : R_f 0.23 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (300 MHz, DMSO-d₆) : δ 10.59 (s, 1H), 9.16 (s, 2H), 8.77 (s, 2H), 8.28 (d, J = 2.1 Hz, 1H), 7.90 (dd, J = 8.1, 2.1 Hz, 1H), 7.89 (d, J = 8.7 Hz, 2H), 7.76 (d, J = 8.7 Hz, 2H), 7.62 (d, J = 8.7 Hz, 1H), 7.46 (s, 1H), 7.25 (d, J = 8.1 Hz, 1H), 7.10 (d, J = 8.7 Hz, 1H), 4.08 (s, 3H), 3.61 (s, 2H), 2.29 (s, 3H), 1.87 (dd, J = 13.8, 5.7 Hz, 2H), 1.80-1.68 (m, 2H), 1.59 (dd, J = 13.8, 5.1 Hz, 2H), 0.89 (d, J = 6.6 Hz, 6H), 0.88 (dd, J = 6.3 Hz, 6H).

Example 41(87)

2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-[(1(S)-(hydroxymethyl)-2(S)-methylbutyl)carbamoyl]benzoic acid methanesulfonate

[0814]



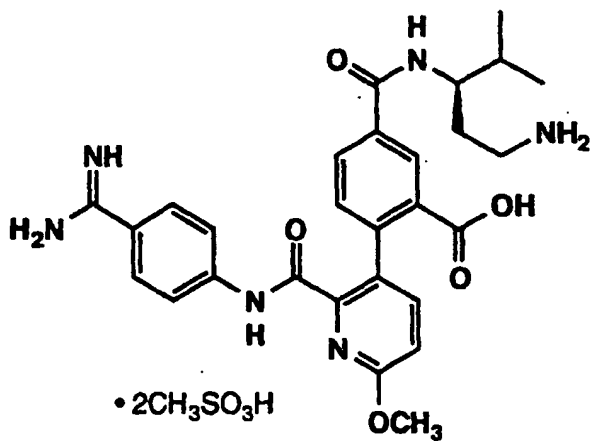
TLC : R_f 0.35 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (300 MHz, d₆-DMSO) : δ 12.8-12.3 (brd, 1H), 10.60 (s, 1H), 9.18 (s, 2H), 8.82 (s, 2H), 8.41 (d, J = 1.8 Hz, 1H), 8.25 (d, J = 8.7 Hz, 1H), 8.04 (dd, J = 8.1, 1.8 Hz, 1H), 7.90 (d, J = 9.0 Hz, 2H), 7.77 (d, J = 9.0 Hz, 2H), 7.64 (d, J = 8.1 Hz, 1H), 7.29 (d, J = 8.1 Hz, 1H), 7.11 (d, J = 8.1 Hz, 1H), 4.09 (s, 3H), 3.88 (m, 1H), 3.52 (m, 1H), 3.00 (m, 1H), 2.31 (s, 3H), 1.74 (m, 1H), 1.50 (m, 1H), 1.18 (m, 1H), 0.90 (d, J = 6.6 Hz, 3H), 0.86 (t, J = 7.5 Hz, 3H).

Example 41(88)

2-[2-(4-amidinophenylcarbamoyl)-6-ethoxy-3-pyridyl]-5-[(1(S)-isopropyl-3-amino propyl)carbamoyl]benzoic acid dimethanesulfonate

[0815]



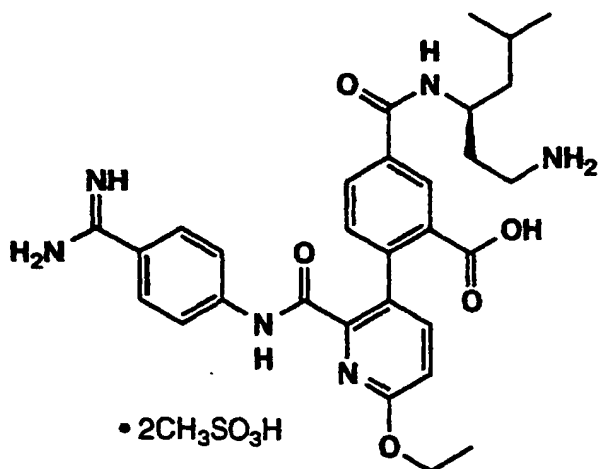
TLC : Rf 0.60 (Ethyl acetate : Acetic acid : Water = 3 : 3 : 1) ;

NMR (300 MHz, d_6 -DMSO) : δ 12.8-12.3 (brd, 1H), 10.58 (s, 1H), 9.19 (s, 2H), 8.91 (s, 2H), 8.45 (d, J = 8.7 Hz, 1H), 8.41 (d, J = 1.8 Hz, 1H), 8.04 (dd, J = 8.1, 1.8 Hz, 1H), 7.88 (d, J = 9.0 Hz, 2H), 7.78 (d, J = 9.0 Hz, 2H), 7.72 (brd, 2H), 7.61 (d, J = 8.4 Hz, 1H), 7.32 (d, J = 8.1 Hz, 1H), 7.19 (dd, J = 19.8, 6.9 Hz, 1H), 7.10 (d, J = 8.4 Hz, 1H), 4.56 (m, 2H), 3.83 (m, 1H), 2.85-2.70 (m, 2H), 2.33 (s, 6H), 1.95-1.70 (m, 3H), 1.41 (t, J = 6.9 Hz, 3H), 0.94 (d, J = 6.0 Hz, 3H), 0.92 (d, J = 6.0 Hz, 3H).

Example 41 (89)

2-[2-(4-amidinophenylcarbamoyl)-6-ethoxy-3-pyridyl]-5-[(1S)-(2-aminoethyl)-3-methylbutyl]carbamoyl]benzoic acid dimethanesulfonate

[0816]



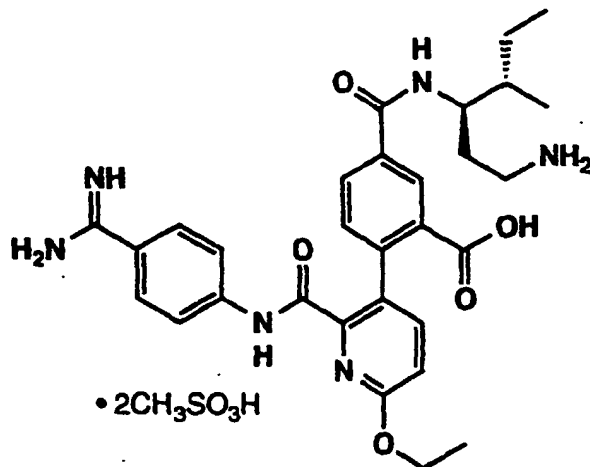
TLC : Rf 0.65 (Ethyl acetate : Acetic acid : Water = 3 : 1 : 1) ;

NMR (300 MHz, d_6 -DMSO) : δ 13.0-12.5 (broad, 1H), 10.57 (s, 1H), 9.20 (brs, 2H), 8.91 (brs, 2H), 8.51 (brd, J = 9.0 Hz, 1H), 8.42 (d, J = 1.8 Hz, 1H), 8.03 (dd, J = 8.0, 1.8 Hz, 1H), 7.89 (d, J = 9.0 Hz, 2H), 7.79 (d, J = 9.0 Hz, 2H), 7.82-7.68 (broad, 3H), 7.62 (d, J = 8.4 Hz, 1H), 7.32 (d, J = 8.0 Hz, 1H), 7.10 (d, J = 8.4 Hz, 1H), 4.56 (brq, J = 7.0 Hz, 2H), 4.21-4.28 (m, 1H), 2.90-2.75 (m, 2H), 2.33 (s, 6H), 1.88-1.57 (m, 4H), 1.41 (t, J = 7.0 Hz, 3H), 1.34-1.22 (m, 1H), 0.91 (d, J = 6.6 Hz, 3H), 0.89 (d, J = 6.9 Hz, 3H).

Example 41(90)

2-[2-(4-amidinophenylcarbamoyl)-6-ethoxy-3-pyridyl]-5-[(1(S)-(2-aminoethyl)-2(S)-methylbutyl)carbamoyl]benzoic acid dimethanesulfonate

[0817]



TLC : R_f 0.64 (Ethyl acetate : Acetic acid : Water = 3 : 1 : 1) ;

NMR (300 MHz, d₆-DMSO) : δ 13.0-12.5 (broad, 1H), 10.57 (s, 1H), 9.20 (brs, 2H), 8.91 (brs, 2H), 8.48 (brd, J = 9.0 Hz, 1H), 8.41 (d, J = 1.8 Hz, 1H), 8.04 (dd, J = 8.0, 1.8 Hz, 1H), 7.89 (d, J = 8.7 Hz, 2H), 7.79 (d, J = 8.7 Hz, 2H), 7.82-7.68 (broad, 3H), 7.62 (d, J = 8.4 Hz, 1H), 7.32 (d, J = 8.0 Hz, 1H), 7.10 (d, J = 8.4 Hz, 1H), 4.56 (brq, J = 7.0 Hz, 2H), 3.98-3.85 (m, 1H), 2.90-2.70 (m, 2H), 2.33 (s, 6H), 1.95-1.58 (m, 3H), 1.41 (t, J = 7.0 Hz, 3H), 1.24-1.08 (m, 1H), 0.91 (d, J = 6.6 Hz, 3H), 0.89 (d, J = 7.2 Hz, 3H).

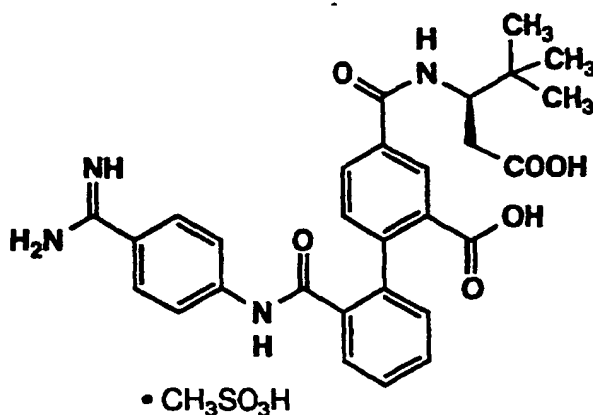
Example 42(1) — 42(7)

[0818] The following compounds were obtained by the same procedure as a series of reaction of Reference Example 8 or Example 11, using a compound prepared in Example 41(5), 41(18), 41(22), 41(23), 41(24), 41(32) or 41(54).

Example 42(1)

2'-(4-amidinophenylcarbamoyl)-4-[(1(S)-carboxymethyl-2, 2-dimethylpropyl) carbamoyl]-2-biphenylcarboxylic acid
methanesulfonate

[0819]



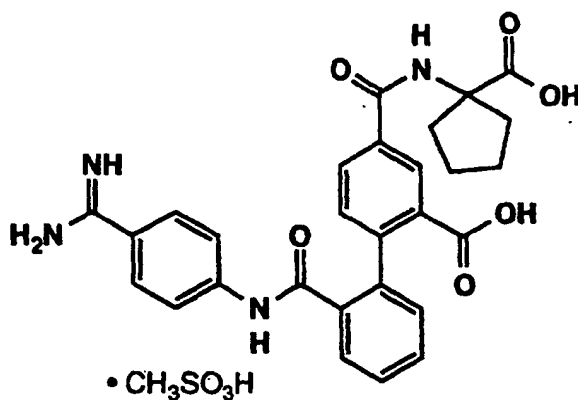
TLC : R_f 0.41 (Ethyl acetate : Acetic acid : Water = 3 : 1 : 1) ;

NMR (d₆-DMSO) : δ 10.6 (1H, s), 9.15 (2H, br s), 8.80 (2H, br s), 8.28 (1H, d, J = 8.8 Hz), 8.26 (1H, s), 7.92 (1H, d, J = 6.0 Hz), 7.73-7.68 (5H, m), 7.60-7.48 (2H, m), 7.33-7.25 (2H, m), 4.29 (1H, t, J = 8.8 Hz), 2.60-2.40 (2H, m), 2.30 (3H, s), 0.89 (9H, s).

Example 42(2)

2'-(4-amidinophenylcarbamoyl)-4-(1-carboxycyclopentylcarbamoyl)-2-biphenyl carboxylic acid methanesulfonate

[0820]



TLC : R_f 0.11 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

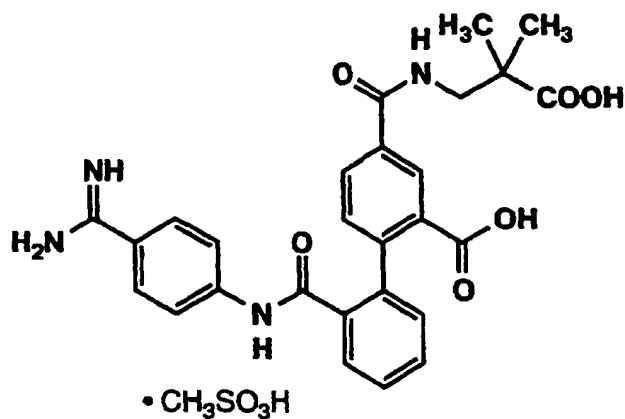
EP 1 078 917 A1

NMR (d_6 -DMSO) : δ 10.5 (s, 1H), 9.15 (br s, 2H), 8.83 (br s, 2H), 8.72 (s, 1H), 8.29 (d, $J = 1.8$ Hz, 1H), 7.96 (dd, $J = 7.8, 1.8$ Hz, 1H), 7.73-7.68 (m, 5H), 7.60-7.50 (m, 2H), 7.31 (d, $J = 7.8$ Hz, 1H), 7.28-7.24 (m, 1H), 2.31 (s, 3H), 2.20-2.00 (m, 4H), 1.80-1.60 (m, 4H).

5 Example 42(3)

2'-(4-amidinophenylcarbamoyl)-4-[(2-carboxy-2, 2-dimethylethyl)carbamoyl]-2-biphenylcarboxylic acid methanesulfonate

10 [0821]



30

TLC : Rf 0.20 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d_6 -DMSO) : δ 10.5 (s, 1H), 9.16 (br s, 2H), 8.87 (br s, 2H), 8.53 (t, $J = 5.0$ Hz, 1H), 8.27 (d, $J = 2.0$ Hz, 1H), 7.94 (dd, $J = 8.4, 2.0$ Hz, 1H), 7.73-7.67 (m, 5H), 7.58-7.52 (m, 2H), 7.32 (d, $J = 8.4$ Hz, 1H), 7.30-7.24 (m, 1H), 3.43 (d, $J = 5.0$ Hz, 2H), 2.32 (s, 3H), 1.10 (s, 6H).

35

40

45

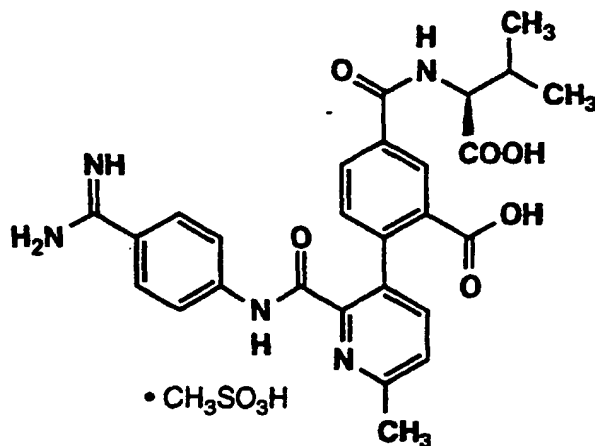
50

55

Example 42(4)

2-[2-(4-amidinophenylcarbamoyl)-6-methyl-3-pyridyl]-5-[(1(S)-carboxy-2-methylpropyl)carbamoyl]benzoic acid methanesulfonate

[0822]



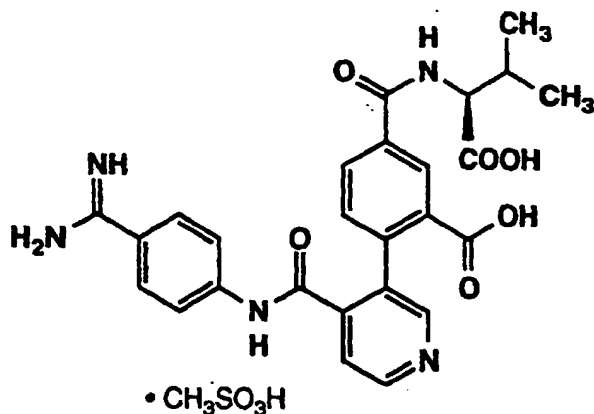
TLC : R_f 0.79 (Ethyl acetate : Acetic acid : Water = 3 : 1 : 1) ;

NMR (d₆-DMSO) : δ 13.0-12.4 (broad, 2H), 10.84 (s, 1H), 9.17 (brs, 2H), 8.90 (brs, 2H), 8.72 (brd, J = 7.5 Hz, 1H), 8.44 (brs, 1H), 8.07 (brd, J = 7.8 Hz, 1H), 7.93 (brd, J = 8.4 Hz, 2H), 7.77 (brd, J = 8.4 Hz, 2H), 7.63 (brd, J = 7.8 Hz, 1H), 7.55 (brd, J = 7.8 Hz, 1H), 7.31 (d, J = 7.8 Hz, 1H), 4.33 (brt, J = 7.5 Hz, 1H), 2.67 (brs, 3H), 2.36 (brs, 3H), 2.30-2.10 (m, 1H), 0.98 (brs, 6H).

Example 42(5)

2-[4-(4-amidinophenylcarbamoyl)-3-pyridyl]-5-[(1(S)-carboxy-2-methylpropyl) carbamoyl]benzoic acid methanesulfonate

[0823]



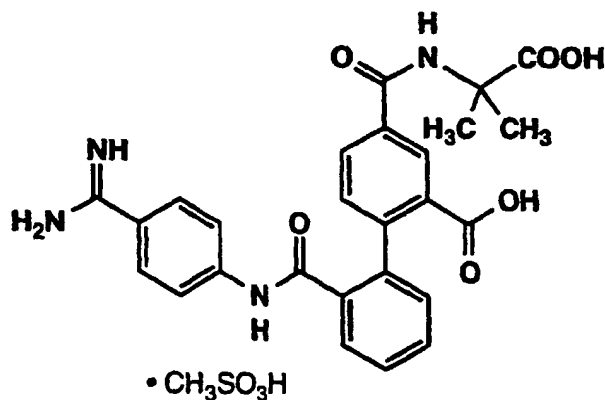
TLC : R_f 0.69 (Ethyl acetate : Acetic acid : Water = 3 : 1 : 1) ;

NMR (d₆-DMSO) : δ 13.2-12.4 (broad, 2H), 10.86 (brs, 1H), 9.16 (brs, 2H), 8.87 (brs, 2H), 8.80-8.68 (m, 2H), 8.52 (brs, 1H), 8.39 (brs, 1H), 8.05 (brd, J = 7.5 Hz, 1H), 7.73 (s, 4H), 7.70 (brd, J = 7.5 Hz, 1H), 7.41 (brd, J = 7.5 Hz, 1H), 4.29 (brt, J = 7.0 Hz, 1H), 2.34 (brs, 3H), 2.30-2.10 (m, 1H), 0.97 (brs, 6H).

Example 42(6)

2'-(4-amidinophenylcarbamoyl)-4-[(1-carboxy-1-methylethyl)carbamoyl]-2-biphenylcarboxylic acid methanesulfonate

[0824]



TLC : R_f 0.51 (Ethyl acetate : Acetic acid : Water = 6 : 2 : 1) ;

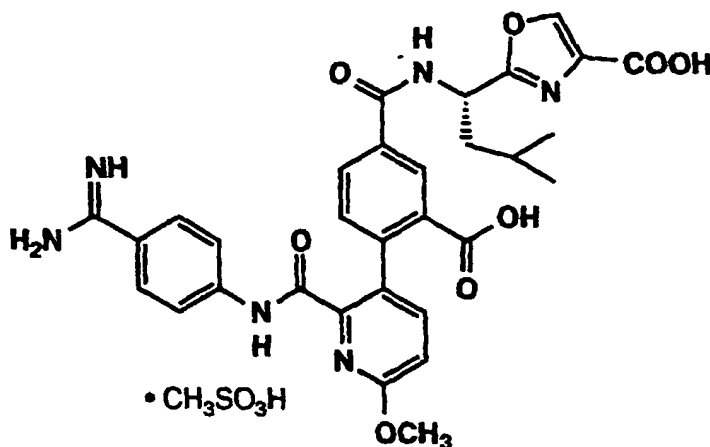
NMR (d₆-DMSO) : δ 12.50 (br, 2H), 10.55 (s, 1H), 9.16 (s, 2H), 8.87 (s, 2H), 8.67 (s, 1H), 8.30 (d, J = 1.8 Hz, 1H),

7.97, (dd, J = 7.8, 1.8 Hz, 1H), 7.74 (s, 4H), 7.70 (dd, J = 7.2, 1.2 Hz, 1H), 7.57 (dt, J = 7.2, 1.2 Hz, 1H), 7.53 (dt, J = 7.2, 1.2 Hz, 1H), 7.33 (d, J = 8.4 Hz, 1H), 7.27 (dd, J = 7.2, 1.2 Hz, 1H), 2.35 (s, 3H), 1.46 (s, 6H).

Example 42(7)

2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-[1(S)-(4-carboxy oxazol-2-yl)-3-methylbutyl]carbamoyl]benzoic acid methanesulfonate

[0825]



TLC : Rf 0.09 (Chloroform : Methanol : Water = 7 : 3 : 0.3) ;

NMR (d_6 -DMSO) : δ 13.2-12.6 (broad, 2H), 10.61 (s, 1H), 9.25 (brd, J = 8.0 Hz, 1H), 9.18 (brs, 2H), 8.86 (brs, 2H), 8.69 (s, 1H), 8.47 (d, J = 1.8 Hz, 1H), 8.07 (dd, J = 7.8, 1.8 Hz, 1H), 7.90 (d, J = 9.0 Hz, 2H), 7.78 (d, J = 9.0 Hz, 2H), 7.65 (d, J = 8.4 Hz, 1H), 7.33 (d, J = 7.8 Hz, 1H), 7.13 (d, J = 8.4 Hz, 1H), 5.38-5.29 (m, 1H), 4.10 (s, 3H), 2.33 (s, 3H), 2.05-1.62 (m, 3H), 0.95 (d, J = 6.3 Hz, 3H), 0.94 (d, J = 6.3 Hz, 3H).

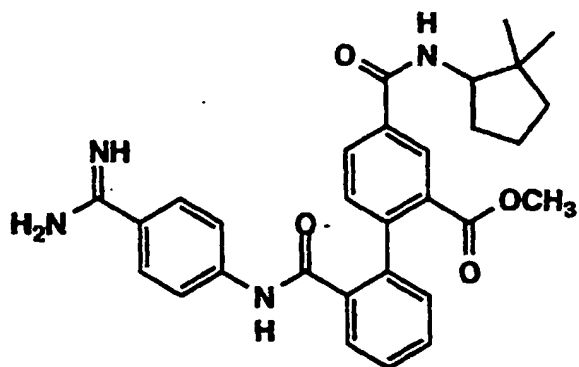
Example 43(1) — 43(6)

[0826] The following compounds were obtained by the same procedure as a series of reaction of Example 1, using a corresponding compound instead of a compound prepared in Reference Example 5.

Example 43(1)

Methyl 2'-(4-amidinophenylcarbamoyl)-4-(2, 2-dimethylcyclopentylcarbamoyl)-2-biphenylcarboxylate

[0827]



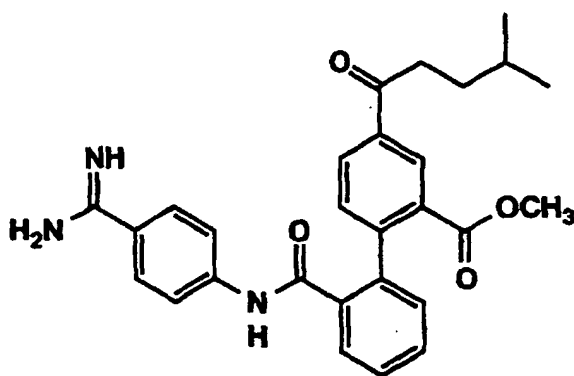
TLC : Rf 0.42 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d_6 -DMSO) : δ 10.63 (1H, br.s), 9.05 (3H, br.d), 8.25-8.15 (2H, m), 8.03 (1H, dd, J = 8.0, 2.0 Hz), 7.74 (4H, like s), 7.69 (1H, dd, J = 8.0, 2.0 Hz), 7.60 (1H, dt, J = 8.0, 2.0 Hz), 7.54 (1H, dt, J = 8.0, 2.0 Hz), 7.40 (1H, d, J = 8.0 Hz), 7.31 (1H, dd, J = 8.0, 2.0 Hz), 4.09 (1H, q, J = 9.0 Hz), 3.54 (3H, s), 1.92 (1H, m), 1.8-1.5 (2H, m), 1.6-1.4 (3H, m), 0.98 (3H, s), 0.87 (3H, s).

Example 43(2)

Methyl 2'-(4-amidinophenylcarbamoyl)-4-(3-methylbutylcarbonyl)-2-biphenylcarboxylate

[0828]



TLC : Rf 0.64 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

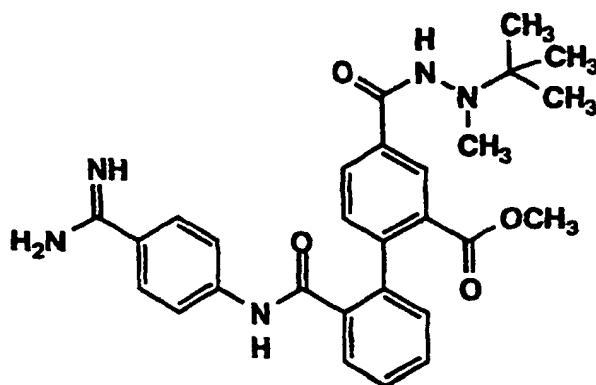
NMR (300 MHz, d_6 -DMSO) : δ 10.67 (br.s, 1H), 9.3-8.9 (br, 3H), 8.28 (d, J = 1.8 Hz, 1H), 8.17 (dd, J = 1.8, 7.8 Hz, 1H), 7.75 (like s, 4H), 7.71 (dd, J = 1.8, 7.8 Hz, 1H), 7.61 (dt, J = 1.8, 7.8 Hz, 1H), 7.55 (dt, J = 1.8, 7.8 Hz, 1H), 7.46 (d, J = 7.8 Hz, 1H), 7.32 (dd, J = 1.8, 7.8 Hz, 1H), 3.54 (s, 3H), 3.05 (t, J = 7.0 Hz, 2H), 1.57 (like septet, J =

7.0 Hz, 1H), 1.51 (q, J = 7.0 Hz, 2H), 0.89 (d, J = 7.0 Hz, 6H).

Example 43(3)

5 Methyl 2'-(4-amidinophenylcarbamoyl)-4-[(N-methyl-N-t-butylamino)carbamoyl]-2-biphenylcarboxylate

[0829]



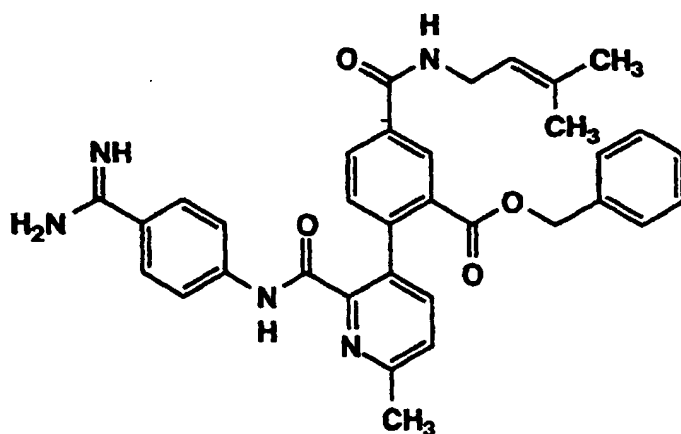
TLC : Rf 0.23 (Chloroform : Methanol : Water = 8 : 2 : 0.2) ;

NMR (200 MHz, CD₃OD) : δ 8.25 (d, J = 2.0 Hz, 1H), 7.94 (dd, J = 8.0, 2.0 Hz, 1H), 7.73-7.65 (m, 5H), 7.61 (dt, J = 8.0, 2.0 Hz, 1H), 7.55 (dt, J = 8.0, 2.0 Hz, 1H), 7.45 (d, J = 8.0 Hz, 1H), 7.30 (dd, J = 8.0, 2.0 Hz, 1H), 3.69 (s, 3H), 2.57 (s, 3H), 1.17 (s, 9H).

Example 43(4)

35 Benzyl 2-[2-(4-amidinophenylcarbamoyl)-6-methyl-3-pyridyl]-5-[(3-methyl-2-butenyl)carbamoyl]benzoate

[0830]



EP 1 078 917 A1

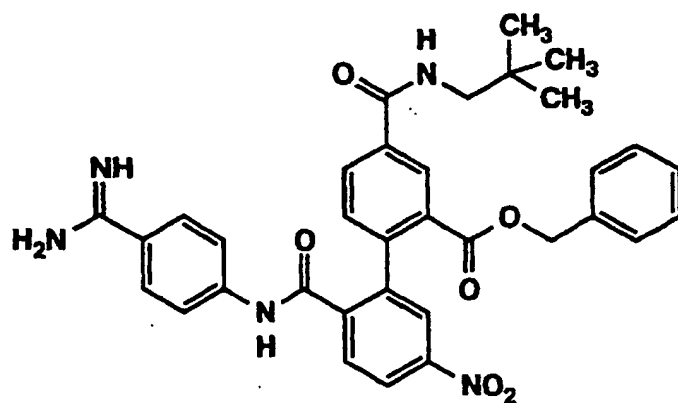
TLC : Rf 0.8 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (300 MHz, CD₃OD) : d 8.51 (d, J = 1.8 Hz, 1H), 8.02 (dd, J = 7.8, 1.8 Hz, 1H), 7.84 (d, J = 9.0 Hz, 2H), 7.75 (d, J = 9.0 Hz, 2H), 7.54 (d, J = 7.8 Hz, 1H), 7.43 (d, J = 7.8 Hz, 1H), 7.31 (d, J = 7.8 Hz, 1H), 7.25-7.17 (m, 3H), 7.05 (brt, J = 6.3 Hz, 1H), 5.32 (brt, J = 7.2 Hz, 1H), 5.00 (d, J = 6.0 Hz, 2H), 4.00 (d, J = 7.2 Hz, 2H), 2.64 (s, 3H), 1.76 (s, 6H).

Example 43(5)

Benzyl 2'-(4-amidinophenylcarbamoyl)-5'-nitro-4-(2, 2-dimethylpropylcarbamoyl)-2-biphenylcarboxylate

[0831]



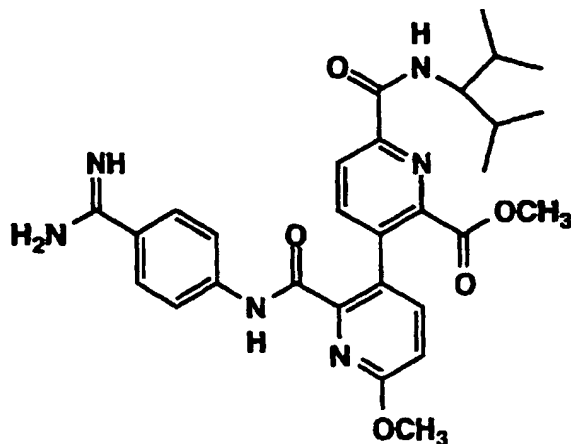
TLC : Rf 0.25 (Chloroform : Methanol : Water = 8 : 2 : 0.2) ;

NMR (200 MHz, CD₃OD) : δ 8.44 (d, J = 2.0 Hz, 1H), 8.21 (dd, J = 8.0, 2.0 Hz, 1H), 8.08 (d, J = 2.0 Hz, 1H), 8.02 (dd, J = 8.0, 2.0 Hz, 1H), 7.78 (d, J = 8.0 Hz, 1H), 7.72 (d, J = 9.0 Hz, 2H), 7.66 (d, J = 9.0 Hz, 2H), 7.47 (d, J = 8.0 Hz, 1H), 7.26-7.21 (m, 3H), 7.15-7.10 (m, 2H), 5.10 (s, 2H), 3.21 (s, 2H), 0.96 (s, 9H).

Example 43(6)

Methyl 3-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-6-[(1-isopropyl-2-methylpropyl)carbamoyl]-2-pyridine-carboxylate

[0832]



TLC : Rf 0.28 (Chloroform : Methanol : Water = 8 : 2 : 0.2) ;

NMR (200 MHz, CD₃OD) : δ 8.32 (d, J = 8.0 Hz, 1H), 7.93 (d, J = 8.0 Hz, 1H), 7.90 (d, J = 9.0 Hz, 2H), 7.78 (d, J = 9.0 Hz, 2H), 7.70 (d, J = 8.4 Hz, 1H), 7.15 (d, J = 8.4 Hz, 1H), 4.17 (s, 3H), 3.74 (t, J = 7.0 Hz, 1H), 3.67 (s, 3H), 2.04 (m, 2H), 0.98 (d, J = 6.6 Hz, 6H), 0.96 (d, J = 6.6 Hz, 6H).

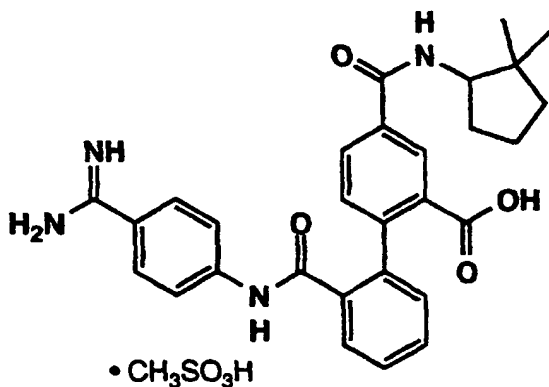
Example 44(1) — 44(6)

[0833] The following compounds were obtained by the same procedure as a series of reaction of Example 11, using a compound prepared in Example 43(1) — 43(6).

Example 44(1)

2'-(4-amidinophenylcarbamoyl)-4-(2, 2-dimethylcyclopentylcarbamoyl)-2-biphenylcarboxylic acid methanesulfonate

[0834]

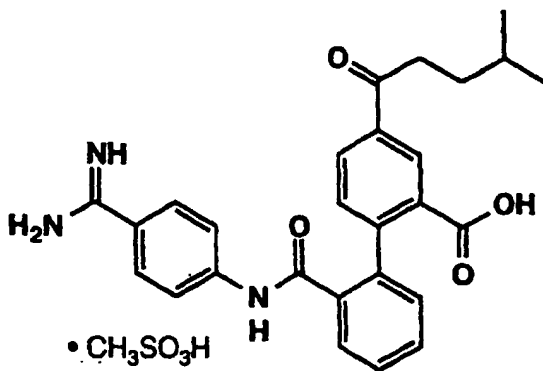
TLC : R_f 0.36 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d₆-DMSO) : δ 12.6-11.8 (1H, br), 10.55 (1H, br.s), 9.14 (2H, br.s), 8.88 (2H, br.s), 8.27 (1H, d, J = 1.8 Hz), 8.19 (1H, d, J = 9.0 Hz), 7.96 (1H, dd, J = 1.8, 8.1 Hz), 7.73 (4H, like s), 7.75-7.65 (1H, m), 7.6-7.5 (2H, m), 7.31 (1H, d, J = 8.1 Hz), 7.26 (1H, dd, J = 1.8, 8.1 Hz), 4.08 (1H, like q, J = 9.0 Hz), 2.36 (3H, s), 1.91 (1H, m), 1.8-1.6 (2H, m), 1.6-1.4 (3H, m), 0.97 (3H, s), 0.87 (3H, s).

Example 44(2)

2'-(4-amidinophenylcarbamoyl)-4-(3-methylbutylcarbonyl)-2-biphenylcarboxylic acid methanesulfonate

[0835]

TLC : R_f 0.33 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

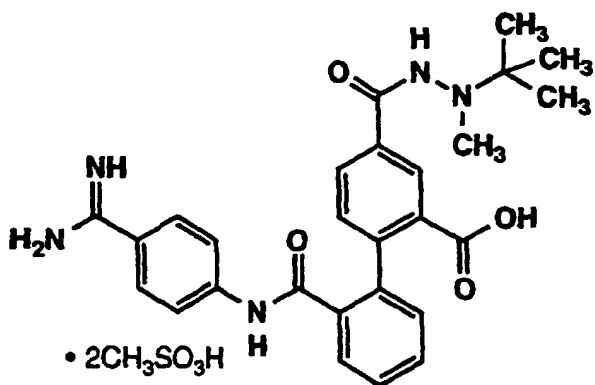
NMR (d₆-DMSO) : δ 12.90 (br.s, 1H), 10.59 (s, 1H), 9.13 (s, 2H), 8.81 (s, 2H), 8.34 (d, J = 1.8 Hz, 1H), 8.10 (dd, J = 1.8, 7.8 Hz, 1H), 7.8-7.65 (m, 5H), 7.65-7.5 (m, 2H), 7.38 (d, J = 7.8 Hz, 1H), 7.28 (dd, J = 1.8, 7.8 Hz, 1H), 3.04

(t, J = 7.0 Hz, 2H), 2.32 (s, 3H), 1.59 (like septet, J = 7.0 Hz, 1H), 1.50 (q, J = 7.0 Hz, 2H), 0.89 (d, J = 7.0 Hz, 6H).

Example 44(3)

2'-(4-amidinophenylcarbamoyl)-4-[(N-methyl-N-t-butylamino)carbamoyl]-2-biphenylcarboxylic acid dimethanesulfonate

[0836]



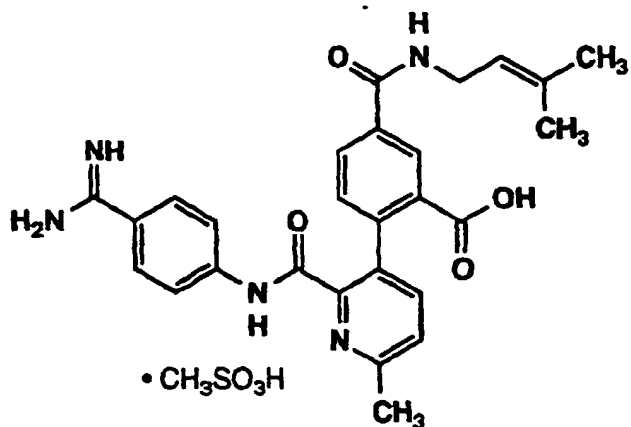
TLC : Rf 0.33 (Chloroform : Methanol : Water = 7 : 3 : 0.3) ;

NMR (d₆-DMSO) : δ 10.65 (s, 1H), 9.23 (s, 2H), 9.01 (s, 2H), 8.32 (d, J = 2.0 Hz, 1H), 8.04 (dd, J = 8.0, 2.0 Hz, 1H), 7.77 (s, 4H), 7.74 (dd, J = 8.0, 2.0 Hz, 1H), 7.59 (dt, J = 8.0, 2.0 Hz, 1H), 7.54 (dt, J = 8.0, 2.0 Hz, 1H), 7.38 (d, J = 8.0 Hz 1H), 7.26 (dd, J = 8.0, 2.0 Hz, 1H), 2.89 (s, 3H), 2.36 (s, 6H), 1.29 (s, 9H).

Example 44(4)

2-[2-(4-amidinophenylcarbamoyl)-6-methyl-3-pyridyl]-5-[(3-methyl-2-butenyl) carbamoyl]benzoic acid methanesulfonate

[0837]



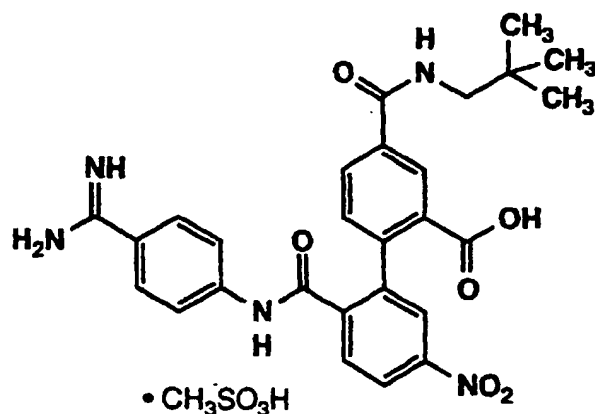
TLC : Rf 0.30 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d_6 -DMSO) : δ 10.83 (s, 1H), 9.20 (s, 2H), 8.90 (s, 2H), 8.78 (t, J = 5.4 Hz, 1H), 8.42 (d, J = 1.8 Hz, 1H), 8.02, (dd, J = 8.4, 1.8 Hz, 1H), 7.92 (d, J = 8.7 Hz, 2H), 7.78 (d, J = 8.7 Hz, 2H), 7.63 (d, J = 7.8 Hz, 1H), 7.55 (d, J = 7.8 Hz, 1H), 7.29 (d, J = 8.4 Hz, 1H), 5.25 (brt, J = 5.4 Hz, 1H), 3.88 (t, J = 5.4 Hz, 2H), 2.67 (s, 3H), 2.33 (s, 3H), 1.69 (s, 6H).

Example 44(5)

2'-(4-amidinophenylcarbamoyl)-5'-nitro-4-(2, 2-dimethylpropylcarbamoyl)-2-biphenylcarboxylic acid methanesulfonate

[0838]



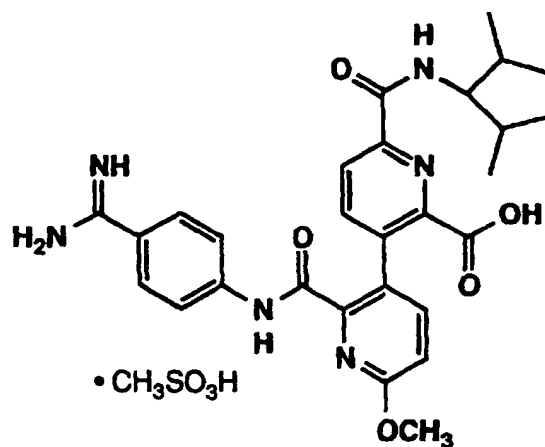
TLC : Rf 0.30 (Chloroform : Methanol : Water = 8 : 2 : 0.2) ;

NMR (d_6 -DMSO) : δ 12.90 (br.s, 1H), 10.84 (s, 1H), 9.15 (s, 2H), 8.78 (s, 2H), 8.59 (br.t, J = 6.3 Hz, 1H), 8.40 (dd, J = 8.0, 2.0 Hz, 1H), 8.39 (d, J = 2.0 Hz, 1H), 8.10 (d, J = 2.0 Hz, 1H), 8.05 (dd, J = 8.0, 2.0 Hz, 1H), 7.96 (d, J = 8.0 Hz, 1H), 7.73 (s, 4H), 7.43 (d, J = 8.0 Hz, 1H), 3.12 (d, J = 6.3 Hz, 2H), 2.33 (s, 3H), 0.91 (s, 9H).

Example 44(6)

3-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-6-[(1-isopropyl-2-methylpropyl)carbamoyl]-2-pyridinecarboxylic acid methanesulfonate

[0839]



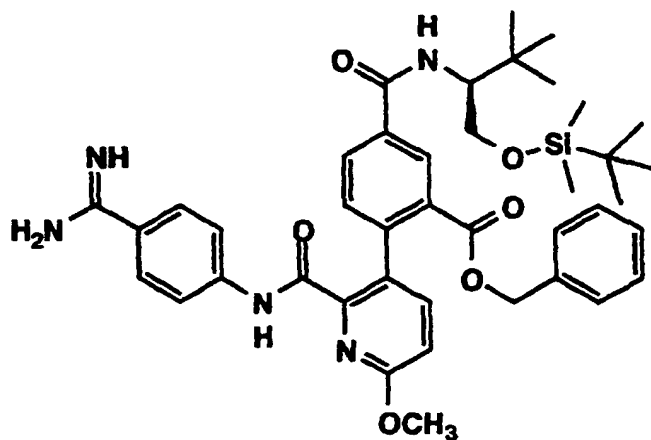
TLC : R_f 0.30 (Chloroform : Methanol : Water = 8 : 2 : 0.2) ;

NMR(d₆-DMSO) : δ 12.95 (br.s, 1H), 10.66 (s 1H), 9.18 (s, 2H), 8.81 (s, 2H), 8.59 (d, J = 10.0 Hz, 1H), 8.27 (d, J = 8.0 Hz, 1H), 7.94 (d, J = 8.0 Hz, 1 H), 7.91 (d, J = 9.0 Hz, 2H), 7.77 (d, J = 9.0 Hz, 2H), 7.76 (d, J = 8.0 Hz, 1H), 7.19 (d, J = 8.0 Hz, 1H), 4.13 (s, 3H), 3.70 (dt, J = 10.0, 7.0 Hz, 1H), 2.31 (s, 3H), 1.98 (m, 2H), 0.91 (d, J = 6.0 Hz, 6H), 0.89 (d, J = 6.0 Hz, 6H).

Reference Example 26

Benzyl 2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-[(1(S)-t-butyl dimethylsilyloxymethyl-2, 2-dimethylpropyl)carbamoyl]benzoate

[0840]



[0841] The title compound was obtained by the same procedure as a series of reaction of Example 1, using 3-[4-(1(S)-t-butyl dimethylsilyloxy-2,2-dimethylpropylcarbamoyl)-2-benzyloxycarbonylphenyl]-6-methoxy-2-pyridinecarboxylic acid which was obtained by the same procedure as a series of reaction of Reference Example 5, using a compound prepared in Reference Example 25.

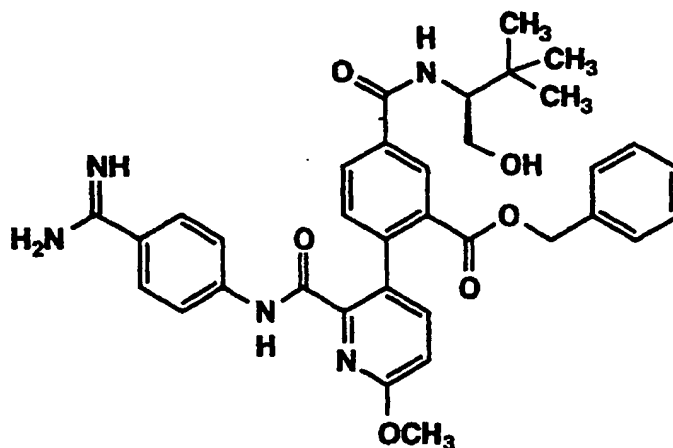
TLC : Rf 0.58 (Chloroform : Methanol : Acetic acid = 20 : 2 : 1) ;

NMR (300 MHz, CD₃OD) : δ 8.46 (d, J = 1.8 Hz, 1H), 7.98 (dd, J = 8.0, 1.8 Hz, 1H), 7.83 (d, J = 9.3 Hz, 2H), 7.77 (d, J = 9.3 Hz, 2H), 7.56 (d, J = 8.4 Hz, 1H), 7.32 (d, J = 8.0 Hz, 1H), 7.28-7.16 (m, 3H), 7.12-7.06 (m, 2H), 6.99 (d, J = 8.4 Hz, 1H), 5.08 (brd, J = 12 Hz, 1H), 4.99 (brd, J = 12 Hz, 1H), 4.07 (dd, J = 8.7, 3.9 Hz, 1H), 3.95 (dd, J = 10.5, 3.9 Hz, 1H), 3.74 (dd, J = 10.5, 8.7 Hz, 1H), 1.03 (s, 9H), 0.86 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H).

Example 45

Benzyl 2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-[(1(S)-hydroxy methyl-2, 2-dimethylpropyl)carbamoyl]benzoate

[0842]



[0843] A solution of a compound prepared in Reference Example 26 (2.15 g) in acetic acid (9 ml) / water (3 ml) was stirred for 16 hours at room temperature. The reaction mixture was concentrated. The residue was purified by column chromatography on silica gel (Chloroform : Methanol : Water = 7 : 3 : 0.3) to give the title compound (1.52 g) having the following physical data.

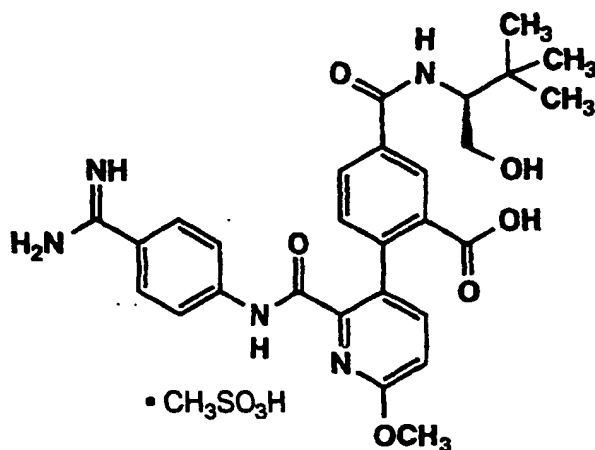
TLC : Rf 0.32 (Chloroform : Methanol : Acetic acid = 20 : 2 : 1) ;

NMR(300 MHz, CD₃OD) : δ 8.52 (d, J = 2.0 Hz, 1H), 8.04 (dd, J = 8.0, 2.0 Hz, 1H), 7.83 (d, J = 9.0 Hz, 2H), 7.77 (d, J = 9.0 Hz, 2H), 7.55 (d, J = 8.4 Hz, 1H), 7.32 (d, J = 8.0 Hz, 1H), 7.28-7.16 (m, 3H), 7.10-7.05 (m, 2H), 6.99 (d, J = 8.4 Hz, 1H), 5.07 (brd, J = 12 Hz, 1H), 4.98 (brd, J = 12 Hz, 1H), 4.09 (dd, J = 9.0, 3.3 Hz, 1H), 4.06 (s, 3H), 3.90 (dd, J = 10.4, 3.3 Hz, 1H), 3.65 (dd, J = 10.4, 9.0 Hz, 1H), 1.02 (s, 9H).

Example 46

2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-[(1(S)-hydroxymethyl-2, 2-dimethylpropyl)carbamoyl]benzoic acid methanesulfonate

[0844]



[0845] The title compound (1.48 g) having the following physical data was obtained by the same procedure as a series of reaction of Example 2, using a compound prepared in Example 45 (1.51 g).

TLC : R_f 0.21 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d₆-DMSO) : δ 13.0-12.4 (broad, 1H), 10.61 (s, 1H), 9.19 (brs, 2H), 8.88 (brs, 2H), 8.41 (d, J = 1.8 Hz, 1H), 8.12 (d, J = 9.0 Hz, 1H), 8.03 (dd, J = 8.0, 1.8 Hz, 1H), 7.90 (d, J = 9.0 Hz, 2H), 7.78 (d, J = 9.0 Hz, 2H), 7.64 (d, J = 8.5 Hz, 1H), 7.30 (d, J = 8.0 Hz, 1H), 7.12 (d, J = 8.0 Hz, 1H), 4.09 (s, 3H), 3.93 (td, J = 9.0, 3.5 Hz, 1H), 3.67 (dd, J = 10.8, 3.5 Hz, 1H), 3.50 (dd, J = 10.8, 9.0 Hz, 1H), 2.33 (s, 3H), 0.92 (s, 9H).

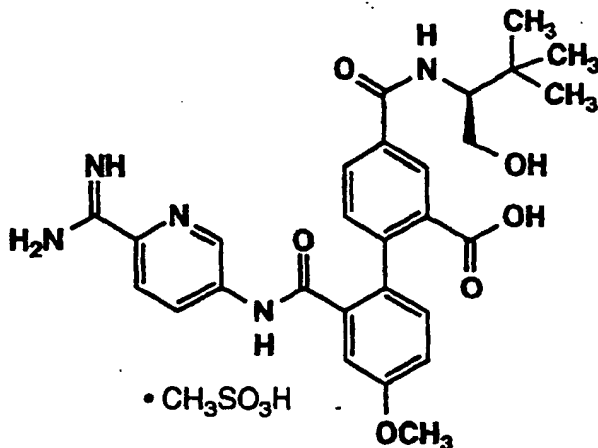
Example 47(1) — 47(32)

[0846] The following compounds were obtained by the same procedure as a series of reaction of Reference Example 26 → Example 45 → Example 46, using a corresponding compound.

Example 47(1)

2'-[(2-amidino-5-pyridyl)carbamoyl]-4'-methoxy-4-[(1(S)-hydroxymethyl-2, 2-dimethylpropyl)carbamoyl]-2-biphenylcarboxylic acid methanesulfonate

[0847]



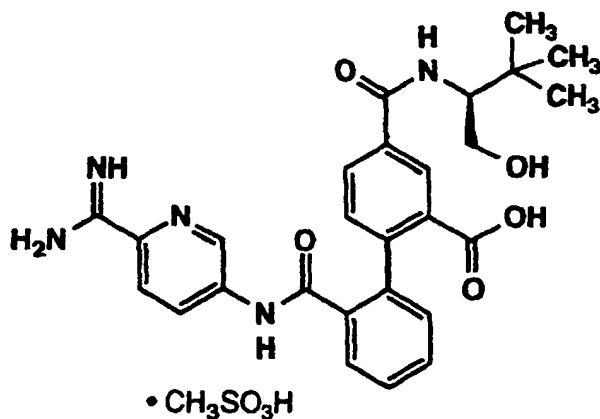
TLC : R_f 0.42 (Chloroform : Methanol : Water = 7 : 3 : 0.3) ;

NMR (d₆-DMSO + 2 drops of CD₃OD) : δ 10.89 (s, 1H), 9.38 (s, 2H), 9.07 (s, 2H), 8.93 (d, J = 2.0 Hz, 1H), 8.30-8.28 (m, 2H), 8.20 (d, J = 8.0 Hz, 1H), 8.07 (d, J = 9.6 Hz, 1H), 7.98 (dd, J = 8.0, 2.0 Hz, 1H), 7.33-7.30 (m, 2H), 7.24 (d, J = 8.0 Hz, 1H), 7.17 (dd, J = 8.0, 2.0 Hz, 1H), 3.90 (s, 3H), 3.67 (dd, J = 11.4, 3.0 Hz, 1H), 3.48 (dd, J = 11.4, 9.3 Hz, 1H), 2.35 (s, 3H), 0.91 (s, 9H).

Example 47(2)

2'-[(2-amidino-5-pyridyl)carbamoyl]-4-[(1(S)-hydroxymethyl-2, 2-dimethylpropyl)carbamoyl]-2-biphenylcarboxylic acid methanesulfonate

[0848]



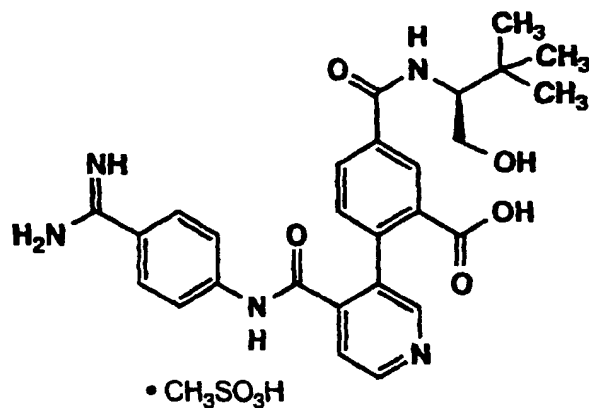
TLC : Rf 0.11 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d_6 -DMSO) : δ 10.9 (s, 1H), 9.37 (br s, 2H), 9.07-9.05 (m, 2H), 8.91 (d, J = 2.6 Hz, 1H), 8.28 (dd, J = 6.6, 2.6 Hz, 1H), 8.18 (d, J = 8.8 Hz, 1H), 8.08 (d, J = 9.4 Hz, 1H), 8.00 (dd, J = 8.0, 1.8 Hz, 1H), 7.77-7.72 (m, 1H), 7.64-7.51 (m, 2H), 7.33 (d, J = 8.0 Hz, 1H), 7.31-7.28 (m, 1H), 3.90-3.85 (m, 1H), 3.80-3.40 (m, 2H), 3.50-3.40 (m, 1H), 2.31 (s, 3H), 0.90 (s, 9H).

Example 47(3)

2-[4-(4-amidinophenylcarbamoyl)-3-pyridyl]-5-[(1(S)-hydroxymethyl-2, 2-dimethylpropyl)carbamoyl]benzoic acid methanesulfonate

[0849]



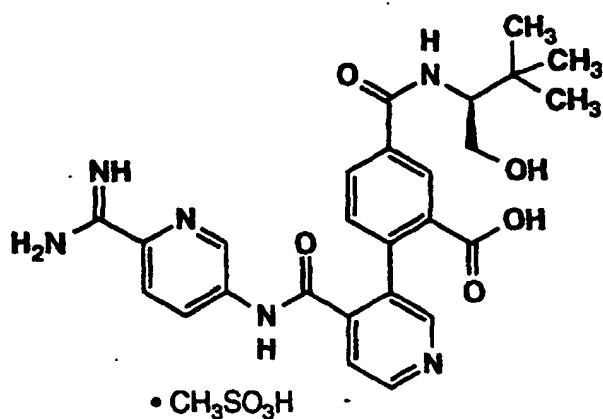
TLC : Rf 0.18 (Chloroform : Methanol : Water = 7 : 3 : 0.3) ;

NMR (d_6 -DMSO) : δ 11.05 (s, 1H), 9.22 (brs, 2H), 8.99 (brs, 2H), 8.90 (d, J = 5.5 Hz, 1H), 8.72 (s, 1H), 8.41 (d, J = 1.5 Hz, 1H), 8.17 (d, J = 9.5 Hz, 1H), 8.07 (dd, J = 8.0, 1.5 Hz, 1H), 7.93 (d, J = 5.5 Hz, 1H), 7.76 (like s, 4H), 7.46 (d, J = 8.0 Hz, 1H), 3.90 (td, J = 9.5, 3.5 Hz, 1H), 3.66 (dd, J = 11.0, 3.5 Hz, 1H), 3.47 (dd, J = 11.0, 9.5 Hz, 1H), 2.36 (s, 3H), 0.90 (s, 9H).

Example 47(4)

2-[4-[(2-amidino-5-pyridyl)carbamoyl]-3-pyridyl]-5-[(1(S)-hydroxymethyl-2, 2-dimethylpropyl)carbamoyl]benzoic acid methanesulfonate

[0850]



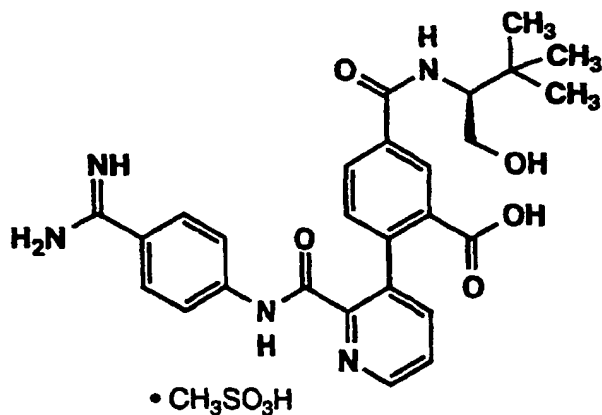
TLC : R_f 0.18 (Chloroform : Methanol : Water = 7 : 3 : 0.3) ;

NMR (d₆-DMSO) : δ 11.38 (s, 1H), 9.44 (brs, 2H), 9.23 (brs, 2H), 8.94 (d, J = 2.0 Hz, 1H), 8.90 (d, J = 5.0 Hz, 1H), 8.70 (s, 1H), 8.40 (d, J = 1.5 Hz, 1H), 8.29 (dd, J = 9.0, 2.0 Hz, 1H), 8.23 (d, J = 9.0 Hz, 1H), 8.16 (d, J = 9.0 Hz, 1H), 8.08 (dd, J = 8.0, 1.5 Hz, 1H), 7.93 (d, J = 5.0 Hz, 1H), 7.47 (d, J = 8.0 Hz, 1H), 3.90 (td, J = 9.0, 3.5 Hz, 1H), 3.66 (dd, J = 11.0, 3.5 Hz, 1H), 3.47 (dd, J = 11.0, 9.0 Hz, 1H), 2.36 (s, 3H), 0.90 (s, 9H).

Example 47(5)

2-[2-(4-amidinophenylcarbamoyl)-3-pyridyl]-5-[(1(S)-hydroxymethyl-2, 2-dimethylpropyl)carbamoyl]benzoic acid methanesulfonate

[0851]



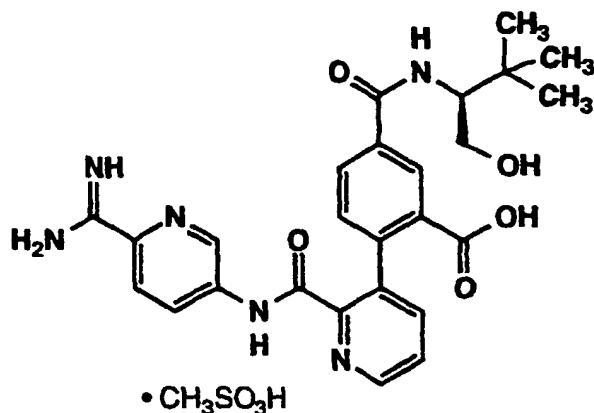
TLC : Rf 0.30 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d_6 -DMSO) : δ 11.00 (s, 1H), 9.20 (s, 2H), 8.94 (s, 2H), 8.73 (dd, J = 4.5, 2.1 Hz, 1H), 8.43 (d, J = 2.1 Hz, 1H),
 8.15 (br.d, J = 9.0 Hz, 1H), 8.08 (dd, J = 8.1, 2.1 Hz, 1H), 7.95 (d, J = 9.0 Hz, 2H), 7.8-7.65 (m, 4H), 7.33 (d, J =
 8.1 Hz, 1H), 5.4-4.6 (br, 2H), 3.94 (td, J = 9.0, 3.6 Hz, 1H), 3.68 (dd, J = 11.1, 3.6 Hz, 1H), 3.51 (dd, J = 11.1, 9.0
 Hz, 1H), 2.37 (s, 3H), 0.93 (s, 9H).

Example 47(6)

2-[2-[(2-amidino-5-pyridyl)carbamoyl]-3-pyridyl]-5-[(1(S)-hydroxymethyl-2, 2-dimethylpropyl)carbamoyl]benzoic acid
 methanesulfonate

[0852]



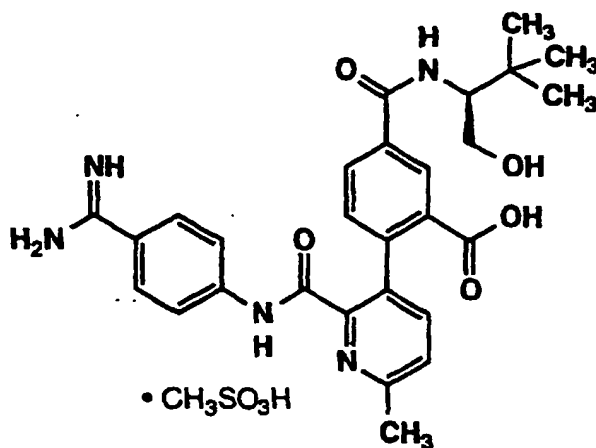
TLC : Rf 0.26 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d_6 -DMSO) : δ 13.0-12.4 (br, 1H), 11.34 (s, 1H), 9.40 (br.s, 2H), 9.12 (d, J = 2.0 Hz, 1H), 9.09 (br.s, 2H), 8.76
 (dd, J = 4.2, 2.1 Hz, 1H), 8.49 (dd, J = 9.0, 2.0 Hz, 1H), 8.44 (d, J = 2.0 Hz, 1H), 8.20 (d, J = 9.0 Hz, 1H), 8.15 (br.d,
 J = 9.3 Hz, 1H), 8.09 (dd, J = 8.0, 2.0 Hz, 1H), 7.8-7.7 (m, 2H), 7.35 (d, J = 8.0 Hz, 1H), 3.94 (td, J = 9.3, 3.3 Hz,
 1H), 3.9-3.7 (br, 1H), 3.69 (dd, J = 10.8, 3.3 Hz, 1H), 3.50 (dd, J = 10.8, 9.3 Hz, 1H), 2.31 (s, 3H), 0.93 (s, 9H).

Example 47(7)

2-[2-(4-amidinophenylcarbamoyl)-6-methyl-3-pyridyl]-5-[(1(S)-hydroxymethyl-2, 2-dimethylpropyl)carbamoyl]benzoic acid methanesulfonate

[0853]



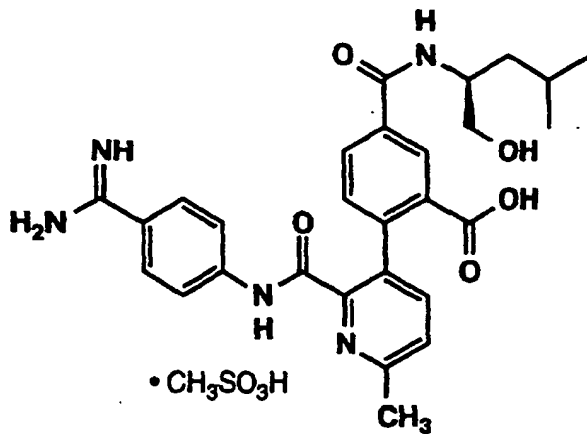
TLC : R_f 0.09 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d₆-DMSO) : δ 10.85 (s, 1H), 9.21 (brs, 2H), 8.94 (brs, 2H), 8.42 (d, J = 1.8 Hz, 1H), 8.14 (d, J = 9.3 Hz, 1H), 8.05 (dd, J = 8.0, 1.8 Hz, 1H), 7.93 (d, J = 9.0 Hz, 2H), 7.78 (d, J = 9.0 Hz, 2H), 7.63 (d, J = 8.0 Hz, 1H), 7.56 (d, J = 8.0 Hz, 1H), 7.30 (d, J = 8.0 Hz, 1H), 3.93 (td, J = 9.3, 3.5 Hz, 1H), 3.68 (dd, J = 11.0, 3.5 Hz, 1H), 3.50 (dd, J = 11.0, 9.3 Hz, 1H), 2.67 (s, 3H), 2.36 (s, 3H), 0.93 (s, 9H).

Example 47(8)

2-[2-(4-amidinophenylcarbamoyl)-6-methyl-3-pyridyl]-5-[[1(S)-hydroxymethyl-3-methylbutyl]carbamoyl]benzoic acid
methanesulfonate

[0854]



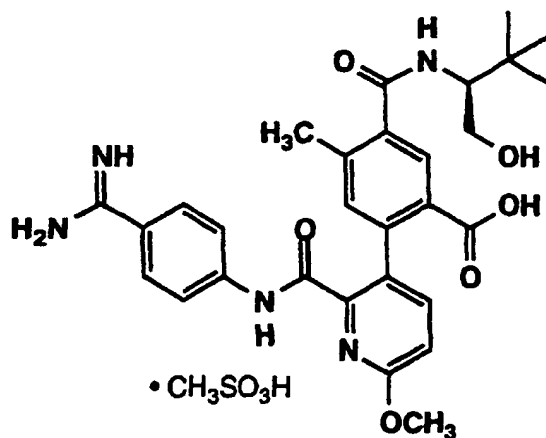
TLC : Rf 0.23 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d_6 -DMSO) : δ 10.8 (s, 1H), 9.21 (br s, 2H), 8.93 (br s, 2H), 8.42 (d, J = 1.8 Hz, 1H), 8.27 (d, J = 8.7 Hz, 1H), 8.05 (dd, J = 8.1, 1.8 Hz, 1H), 7.93 (d, J = 8.1 Hz, 2H), 7.78 (d, J = 8.1 Hz, 2H), 7.63 (d, J = 8.1 Hz, 1H), 7.55 (d, J = 8.1 Hz, 1H), 7.29 (d, J = 8.1 Hz, 1H) 4.20-4.10 (m, 1H), 3.47-3.33 (m, 2H), 2.67 (s, 3H), 2.36 (s, 3H), 1.70-1.30 (m, 3H), 0.91-0.87 (m, 6H).

Example 47(9)

2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-4-methyl-5-[(1(S)-hydroxymethyl-2, 2-dimethylpropyl)carbamoyl]benzoic acid methanesulfonate

[0855]



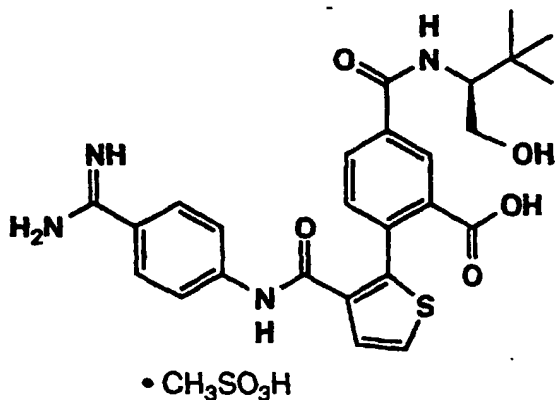
TLC : Rf 0.37 (Chloroform : Methanol : Water = 8 : 2 : 0.2) ;

NMR (d₆-DMSO) : δ 10.59 (s, 1H), 9.21 (s, 2H), 8.89 (s, 2H), 8.07 (d, J = 9.0 Hz, 1H), 7.91 (d, J = 9.0 Hz, 2H), 7.89 (s, 1H), 7.79 (d, J = 9.0 Hz, 2H), 7.58 (d, J = 8.0 Hz, 1H), 7.10 (d, J = 8.0 Hz, 1H), 7.08 (s, 1H), 4.09 (s, 3H), 3.40 (t, J = 9.0 Hz, 1H), 2.38 (s, 3H), 2.33 (s, 3H), 0.94 (s, 9H).

Example 47(10)

2-[3-(4-amidinophenylcarbamoyl)-2-thienyl]-5-[(1(S)-hydroxymethyl-2, 2-dimethylpropyl)carbamoyl]benzoic acid methanesulfonate

[0856]



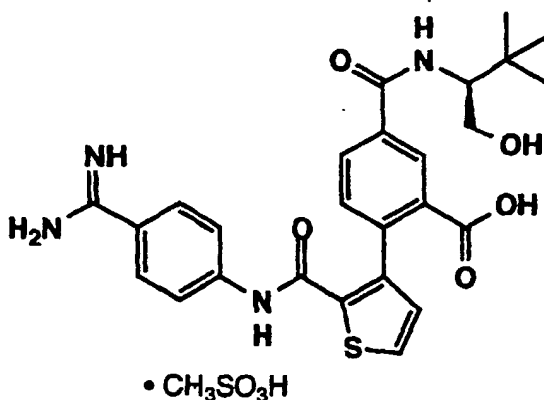
TLC : Rf 0.31 (Chloroform : Methanol : Water = 8 : 2 : 0.2) ;

NMR (d_6 -DMSO) : δ 10.32 (s, 1H), 9.18 (s, 2H), 8.89 (s, 2H), 8.30 (d, J = 2.0 Hz, 1H), 8.13 (br.d, J = 9.3 Hz, 1H),
 8.01 (dd, J = 8.0, 2.0 Hz, 1H), 7.83 (d, J = 9.0 Hz, 2H), 7.75 (d, J = 9.0 Hz, 2H), 7.72 (d, J = 5.6 Hz, 1H), 7.65 (d, J
 = 5.6 Hz, 1H), 7.48 (d, J = 8.0 Hz, 1H), 3.90 (m, 1H), 3.67 (dd, J = 11.5, 3.3 Hz, 1H), 3.48 (dd, J = 11.5, 9.0 Hz, 1H),
 2.33 (s, 3H), 0.91 (s, 9H).

Example 47(11)

2-[2-(4-amidinophenylcarbamoyl)-3-thienyl]-5-[(1(S)-hydroxymethyl-2, 2-dimethylpropyl)carbamoyl]benzoic acid meth-
 anesulfonate

[0857]



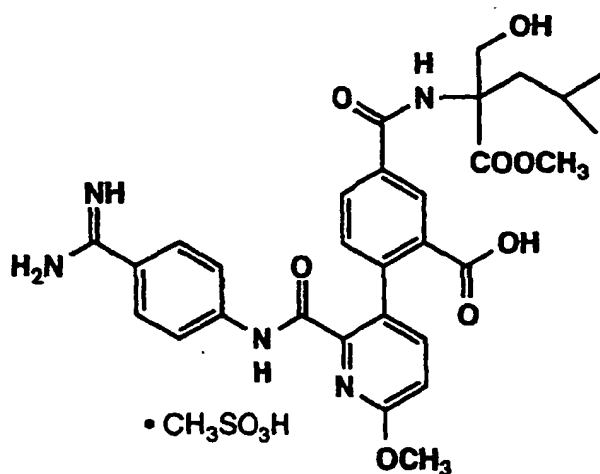
TLC : Rf 0.35 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d_6 -DMSO) : δ 13.0-12.4 (br, 1H), 10.18 (s, 1H), 9.18 (s, 2H), 8.87 (s, 2H), 8.30 (d, J = 1.8 Hz, 1H), 8.09 (br.d,
 J = 9.6 Hz, 1H), 8.02 (dd, J = 8.0, 1.8 Hz, 1H), 7.84 (d, J = 5.0 Hz, 1H), 7.74 (d, J = 9.0 Hz, 2H), 7.70 (d, J = 9.0
 Hz, 2H), 7.41 (d, J = 8.0 Hz, 1H), 7.11 (d, J = 5.0 Hz, 1H), 3.91 (m, 1H), 3.66 (m, 1H), 3.65-3.45 (br, 1H), 3.48 (m,
 1H), 2.32 (s, 3H), 0.91 (s, 9H).

Example 47(12)

2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-[(1-hydroxymethyl-1-methoxycarbonyl-3-methylbutyl)carbamoyl]benzoic acid methanesulfonate

[0858]



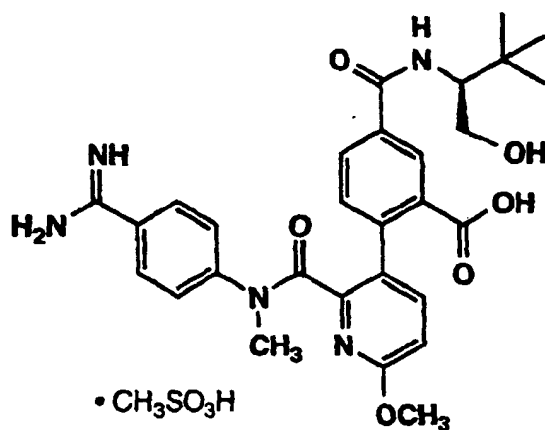
TLC : Rf 0.54 (Chloroform : Methanol : Water = 8 : 2 : 0.2) ;

NMR (d_6 -DMSO) : δ 12.75 (br.s, 1H), 10.61 (s, 1H), 9.19 (s, 2H), 8.86 (s, 2H), 8.38 (d, J = 2.0 Hz, 1H), 8.25 (s, 1H), 8.00 (dd, J = 8.0, 2.0 Hz, 1H), 7.90 (d, J = 9.0 Hz, 2H), 7.78 (d, J = 9.0 Hz, 2H), 7.65 (d, J = 8.0 Hz, 1H), 7.31 (d, J = 8.0 Hz, 1H), 7.13 (d, J = 8.0 Hz, 1H), 4.10 (s, 3H), 3.82 (s, 2H), 3.62 (s, 3H), 2.31 (s, 3H), 1.96 (dd, J = 13.6, 6.3 Hz, 1H), 1.87 (dd, J = 13.6, 6.3 Hz, 1H), 1.65 (m, 1H), 0.87 (d, J = 5.7 Hz, 3H), 0.85 (d, J = 5.7 Hz, 3H).

Example 47(13)

2-[2-[N-(4-amidinophenyl)-N-methylcarbamoyl]-6-methoxy-3-pyridyl]-5-[(1(S)-hydroxymethyl-2, 2-dimethylpropyl)carbamoyl]benzoic acid methanesulfonate

[0859]



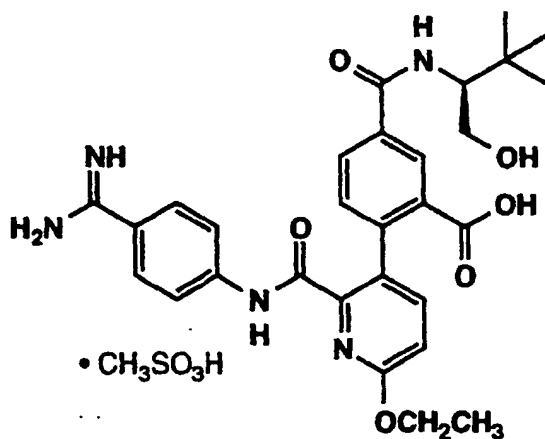
TLC : R_f 0.35 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (CD₃OD) : δ 8.48 (d, J = 2.0 Hz, 1H), 8.01 (dd, J = 8.2, 2.0 Hz, 1H), 7.67 (d, J = 8.4 Hz, 2H), 7.54 (d, J = 8.4 Hz, 1H), 7.34 (d, J = 8.4 Hz, 1H), 7.20 (d, J = 8.4 Hz, 2H), 6.82 (d, J = 8.4 Hz, 1H), 4.09 (dd, J = 9.0, 3.6 Hz, 1H), 3.90 (dd, J = 11.6, 3.6 Hz, 1H), 3.83 (s, 3H), 3.43 (dd, J = 11.6, 9.0 Hz, 1H), 3.28 (s, 3H), 2.70 (s, 3H), 1.02 (s, 9H).

Example 47(14)

2-[2-(4-amidinophenylcarbamoyl)-6-ethoxy-3-pyridyl]-5-[(1(S)-hydroxymethyl-2, 2-dimethylpropyl)carbamoyl]benzoic acid methanesulfonate

[0860]



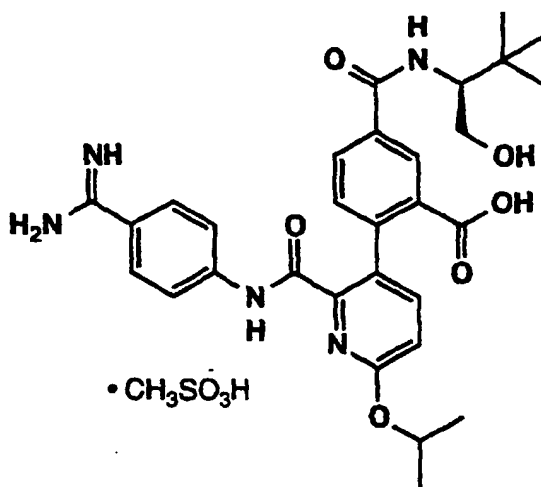
TLC : Rf 0.38 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d_6 -DMSO) : δ 10.6 (s, 1H), 9.19 (br s, 2H), 8.87 (br s, 2H), 8.40 (d, J = 1.5 Hz, 1H), 8.11 (d, J = 9.3 Hz, 1H),
 8.03 (dd, J = 8.1, 1.5 Hz, 1H), 7.89 (d, J = 9.0 Hz, 2H), 7.77 (d, J = 9.0 Hz, 2H), 7.63 (d, J = 8.7 Hz, 1H), 7.29 (d, J
 = 8.1 Hz, 1H), 7.10 (d, J = 8.7 Hz, 1H), 4.56 (q, J = 6.9 Hz, 2H), 3.93 (dt, J = 3.9, 9.3 Hz, 1H), 3.68 (dd, J = 11.1,
 3.9 Hz, 1H), 3.53-3.34 (m, 1H), 2.31 (s, 3H), 1.41 (t, J = 6.9 Hz, 3H), 0.92 (s, 9H).

Example 47(15)

2-[2-(4-amidinophenylcarbamoyl)-6-isopropoxy-3-pyridyl]-5-[(1(S)-hydroxy methyl-2, 2-dimethylpropyl)car-
 bamoyl]benzoic acid methanesulfonate

[0861]



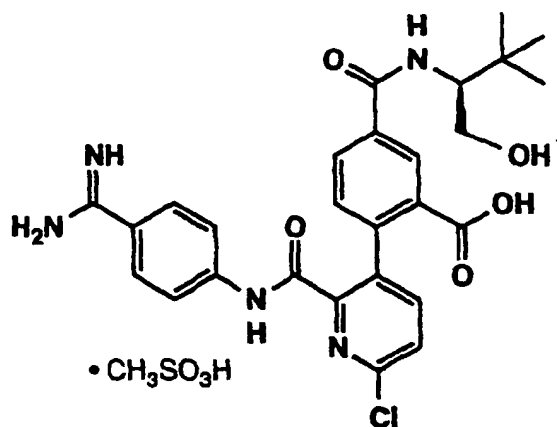
TLC : Rf 0.50 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d_6 -DMSO) : δ 10.5 (s, 1H), 9.19 (br s, 2H), 8.85 (br s, 2H), 8.40 (d, J = 2.1 Hz, 1H), 8.11 (d, J = 9.6 Hz, 1H),
 8.03 (dd, J = 8.1, 2.1 Hz, 1H), 7.88 (d, J = 8.7 Hz, 2H), 7.77 (d, J = 8.7 Hz, 2H), 7.61 (d, J = 8.4 Hz, 1H), 7.30 (d, J
 = 8.1 Hz, 1H), 7.04 (d, J = 8.4 Hz, 1H), 5.59 (quintet, J = 6.0 Hz, 1H), 3.93 (dt, J = 3.9, 9.0 Hz, 1H), 3.68 (dd, J =
 11.1, 3.9 Hz, 1H), 3.53-3.34 (m, 1H), 2.31 (s, 3H), 1.38 (d, J = 6.0 Hz, 6H), 0.92 (s, 9H).

Example 47(16)

2-[2-(4-amidinophenylcarbamoyl)-6-chloro-3-pyridyl]-5-[(1(S)-hydroxymethyl-2, 2-dimethylpropyl)carbamoyl]benzoic acid methanesulfonate

[0862]



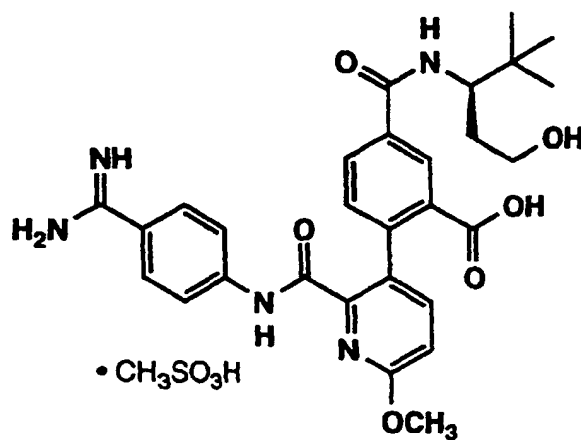
TLC : R_f 0.40 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d₆-DMSO) : δ 10.86 (s, 1H), 9.19 (s, 2H), 8.89 (s, 2H), 8.43 (d, J = 12 Hz, 1H), 8.15 (d, J = 9.0 Hz, 1H), 8.07 (dd, J = 8.1, 1.2 Hz, 1H), 7.89 (d, J = 8.7 Hz, 2H), 7.84 (d, J = 8.7 Hz, 1H), 7.80 (J = 8.7 Hz, 1H), 7.75 (d, J = 8.7 Hz, 2H), 7.35 (d, J = 8.1 Hz, 1H), 3.93 (dt, J = 3.3, 9.0 Hz, 1H), 3.67 (dd, J = 11.4, 3.3 Hz, 1H), 3.45 (m, 1H), 2.32 (s, 3H), 0.92 (s, 9H).

Example 47(17)

2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-[(1(S)-(2-hydroxy ethyl)-2, 2-dimethylpropyl)carbamoyl]benzoic acid methanesulfonate

[0863]



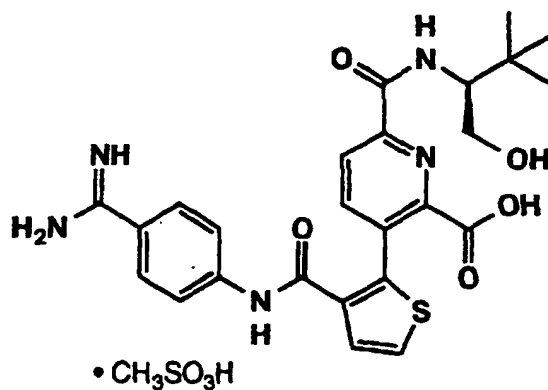
TLC : R_f 0.71 (Chloroform : Ethyl acetate : Water = 3 : 1 : 1) ;

NMR (d₆-DMSO) : δ 12.70 (brs, 1H), 10.62 (s, 1H), 9.18 (s, 2H), 8.79 (s, 2H), 8.40 (d, J = 1.8 Hz, 1H), 8.13 (d, J = 9.3 Hz, 2H), 8.02 (dd, J = 7.8, 1.8 Hz, 1H), 7.92 (d, J = 9.0 Hz, 2H), 7.78 (d, J = 9.0 Hz, 2H), 7.65 (d, J = 8.1 Hz, 1H), 7.30 (d, J = 7.8 Hz, 1H), 7.13 (d, J = 8.1 Hz, 1H), 4.35 (m, 1H), 4.11 (s, 3H), 3.94 (t, J = 10.8 Hz, 1H), 3.42 (t, J = 9.9 Hz, 1H), 2.31 (s, 3H), 1.74 (m, 1H), 1.65 (m, 1H), 0.93 (s, 9H).

Example 47(18)

3-[3-(4-amidinophenylcarbamoyl)-2-thienyl]-6-[(1(S)-hydroxymethyl-2, 2-dimethylpropyl)carbamoyl]-2-pyridinecarboxylic acid methanesulfonate

[0864]



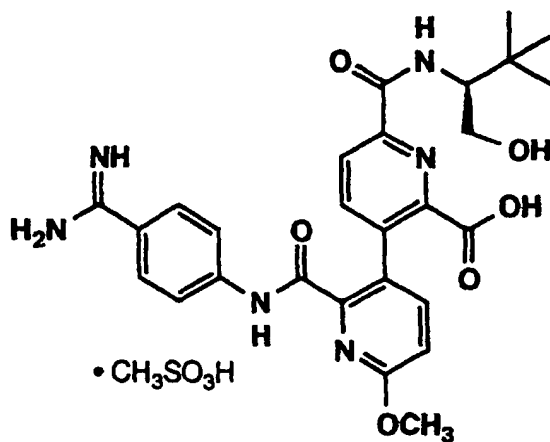
TLC : Rf 0.31 (Chloroform : Methanol : Water = 8 : 2 : 0.2) ;

NMR (d_6 -DMSO) : δ 10.45 (s, 1H), 9.20 (s, 2H), 8.93 (s, 2H), 8.50 (d, J = 10.2 Hz, 1H), 8.21 (d, J = 8.0 Hz, 1H), 8.09 (d, J = 8.0 Hz, 1H), 7.86 (d, J = 9.0 Hz, 2H), 7.82 (d, J = 5.7 Hz, 1H), 7.77 (d, J = 9.0 Hz, 2H), 7.76 (d, J = 5.7 Hz, 1H), 3.89 (m, 1H), 3.71 (dd, J = 11.4, 3.3 Hz, 1H), 3.55 (dd, J = 11.4, 8.0 Hz, 1H), 2.35 (s, 3H), 0.94 (s, 9H).

Example 47(19)

3-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-6-[(1(S)-hydroxymethyl-2, 2-dimethylpropyl)carbamoyl]-2-pyridinecarboxylic acid methanesulfonate

[0865]



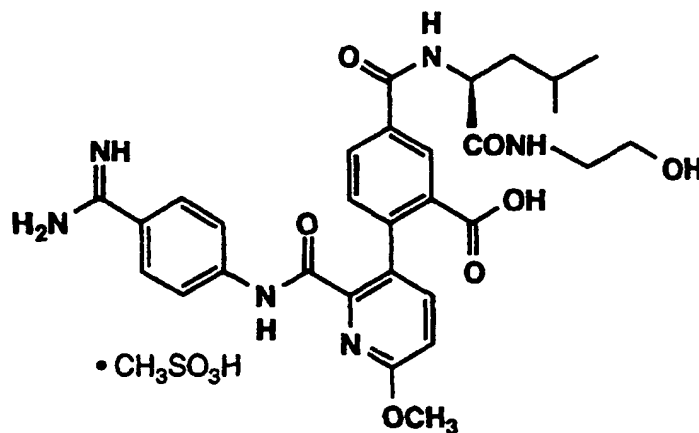
TLC : Rf 0.33 (Chloroform : Methanol : Water = 8 : 2 : 0.2) ;

NMR (d_6 -DMSO) : δ 12.95 (br.s, 1H), 10.66 (s, 1H), 9.21 (s, 2H), 8.91 (s, 2H), 8.67 (d, J = 10.0 Hz, 1H), 8.26 (d, J = 8.0 Hz, 1H), 7.94 (d, J = 8.0 Hz, 1H), 7.91 (d, J = 9.0 Hz, 2H), 7.79 (d, J = 9.0 Hz, 2H), 7.76 (d, J = 8.0 Hz, 1H), 7.19 (d, J = 8.0 Hz, 1H), 4.12 (s, 3H), 3.93 (m, 1H), 3.74 (dd, J = 11.0, 3.6 Hz, 1H), 3.56 (dd, J = 11.0, 8.7 Hz, 1H), 2.33 (s, 3H), 0.95 (s, 9H).

Example 47(20)

2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-[[1(S)-(2-hydroxy ethylcarbamoyl)-3-methylbutyl]carbamoyl]benzoic acid methanesulfonate

[0866]



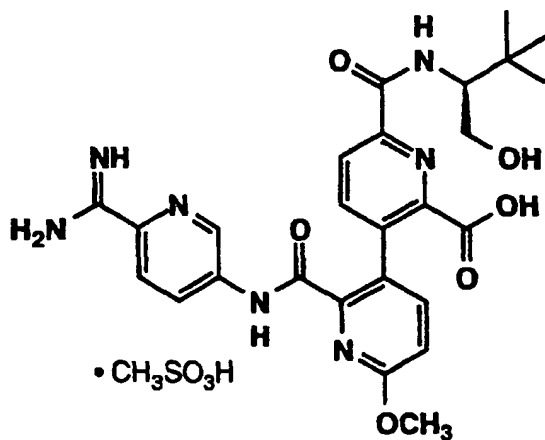
TLC : R_f 0.16 (Chloroform : Methanol : Water = 8 : 2 : 0.2) ;

NMR (d₆-DMSO) : δ 12.71 (br, 1H), 10.60 (s, 1H), 9.25 (s, 2H), 9.01 (s, 2H), 8.70 (d, J = 5.4 Hz, 1H), 8.45 (d, J = 2.1 Hz, 1H), 8.08 (dd, J = 8.1, 2.1 Hz, 1H), 7.97 (t, J = 5.7 Hz, 1H), 7.89 (d, J = 8.7 Hz, 2H), 7.80 (d, J = 8.7 Hz, 2H), 7.63 (d, J = 8.4 Hz, 1H), 7.29 (d, J = 8.1 Hz, 1H), 7.10 (d, J = 8.4 Hz, 1H), 4.53 (m, 1H), 3.44-3.20 (m, 2H), 3.18-3.04 (m, 2H), 2.33 (s, 3H), 1.75-1.62 (m, 2H), 1.51 (m, 1H), 0.89 (d, J = 6.3 Hz, 3H), 0.87 (d, J = 6.0 Hz, 3H).

Example 47(21)

3-[2-(2-amidino-5-pyridylcarbamoyl)-6-methoxy-3-pyridyl]-6-[(1(S)-hydroxy methyl-2, 2-dimethylpropyl)carbamoyl]-2-pyridinecarboxylic acid methanesulfonate

[0867]



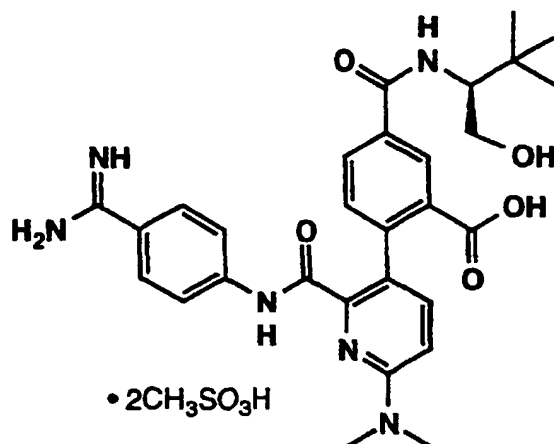
TLC : R_f 0.22 (Chloroform : Methanol : Water = 8 : 2 : 0.2) ;

NMR (d₆-DMSO) : δ 12.95 (br.s, 1H), 10.92 (s 1H), 9.40 (s, 2H), 9.14 (s, 2H), 9.05 (d, J = 2.0 Hz, 1H), 8.66 (d, J = 10.0 Hz, 1H), 8.42 (dd, J = 9.0, 2.0 Hz, 1H), 8.27 (d, J = 8.0 Hz, 1H), 8.22 (d, J = 9.0 Hz, 1H), 7.96 (d, J = 8.0 Hz, 1H), 7.78 (br.d, J = 8.4 Hz, 1H), 7.22 (d, J = 8.4 Hz, 1H), 4.13 (s, 3H), 3.92 (m, 1H), 3.76 (m, 1H), 3.56 (m, 1H), 2.32 (s, 3H), 0.95 (s, 9H).

Example 47(22)

2-[2-(4-amidinophenylcarbamoyl)-6-dimethylamino-3-pyridyl]-5-[(1(S)-hydroxy methyl-2, 2-dimethylpropyl)carbamoyl]benzoic acid dimethanesulfonate

[0868]



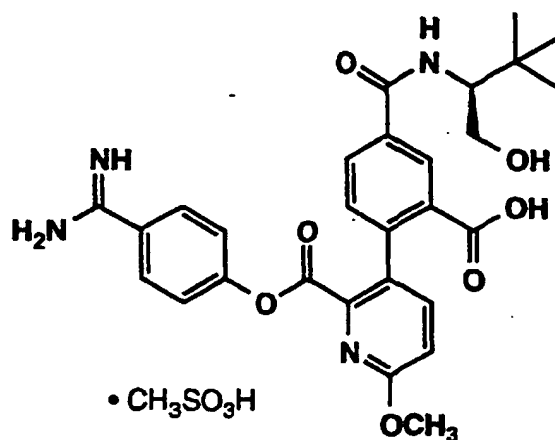
TLC : R_f 0.21 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d₆-DMSO) : δ 10.6 (s, 1H), 9.17 (br s, 2H), 8.82 (br s, 2H), 8.35 (d, J = 2.1 Hz, 1H), 8.07 (d, J = 9.6 Hz, 1H), 7.99 (dd, J = 8.1, 2.1 Hz, 1H), 7.89 (d, J = 9.0 Hz, 2H), 7.76 (d, J = 9.0 Hz, 2H), 7.40 (d, J = 8.7 Hz, 1H), 7.25 (d, J = 8.1 Hz, 1H), 6.93 (d, J = 8.7 Hz, 1H), 3.92 (dt, J = 3.6, 9.0 Hz, 1H), 3.88-3.54 (m, 1H), 3.49 (dd, J = 10.5, 9.0 Hz, 1H), 3.17 (s, 6H), 2.33 (s, 6H), 0.92 (s, 9H).

Example 47(23)

2-[2-(4-amidinophenoxy)carbonyl]-6-methoxy-3-pyridyl]-5-[(1(S)-hydroxymethyl-2, 2-dimethylpropyl)carbamoyl]benzoic acid methanesulfonate

[0869]



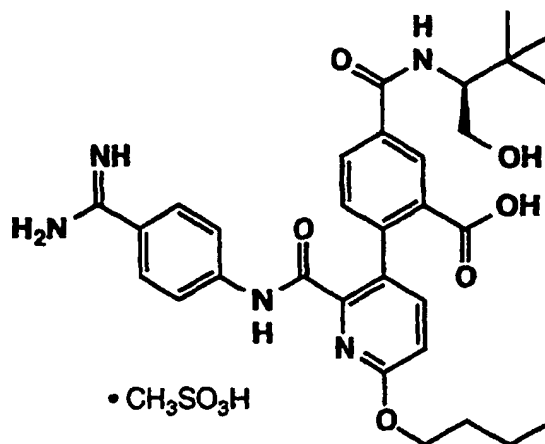
TLC : R_f 0.13 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d₆-DMSO) : δ 13.01 (brs, 1H), 9.30 (brs, 2H), 8.99 (brs, 2H), 8.40 (d, J = 1.8 Hz, 1H), 8.12 (brd, J = 9.3 Hz, 1H), 8.08 (brd, J = 8.0 Hz, 1H), 7.80 (d, J = 8.7 Hz, 2H), 7.74 (d, J = 8.4 Hz, 1H), 7.42 (d, J = 8.0 Hz, 1H), 7.20 (d, J = 8.4 Hz, 1H), 7.19 (d, J = 8.7 Hz, 2H), 4.60-4.30 (broad, 1H), 3.99 (s, 3H), 3.90 (dt, J = 3.3, 9.3 Hz, 1H), 3.66 (dd, J = 10.8, 3.3 Hz, 1H), 3.47 (dd, J = 10.8, 9.3 Hz, 1H), 2.30 (s, 3H), 0.90 (s, 9H).

Example 47(24)

2-[2-(4-amidinophenylcarbamoyl)-6-butoxy-3-pyridyl]-5-[(1(S)-hydroxymethyl-2, 2-dimethylpropyl)carbamoyl]benzoic acid methanesulfonate

[0870]



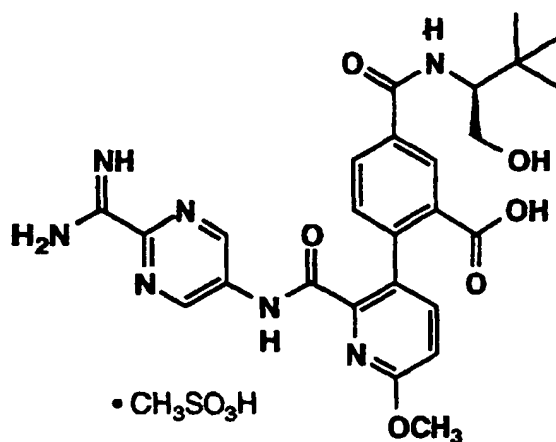
TLC : R_f 0.29 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d₆-DMSO) : δ 10.6 (s, 1H), 9.18 (br s, 2H), 8.82 (br s, 2H), 8.40 (d, J = 1.8 Hz, 1H), 8.11 (d, J = 6.3 Hz, 1H), 8.03 (dd, J = 8.1, 6.3 Hz, 1H), 7.89 (d, J = 9.0 Hz, 2H), 7.77 (d, J = 9.0 Hz, 2H), 7.63 (d, J = 8.4 Hz, 1H), 7.29 (d, J = 8.1 Hz, 1H), 7.10 (d, J = 8.4 Hz, 1H), 4.51 (t, J = 6.6 Hz, 2H), 3.93 (dt, J = 3.3, 9.0 Hz, 1H), 3.68 (dd, J = 3.3, 8.1 Hz, 1H), 3.53-3.34 (m, 1H), 2.30 (s, 3H), 1.78 (quintet, J = 6.6 Hz, 2H), 1.49 (sextet, J = 6.6 Hz, 2H), 0.97 (t, J = 6.6 Hz, 3H), 0.92 (s, 9H).

Example 47(25)

2-[2-(2-amidinopyrimidin-5-yl)carbamoyl-6-methoxy-3-pyridyl]-5-[(1(S)-hydroxy methyl-2, 2-dimethylpropyl)carbamoyl]benzoic acid methanesulfonate

[0871]



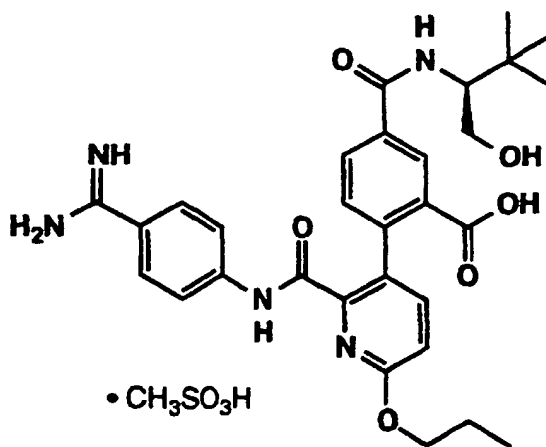
TLC : R_f 0.24 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d₆-DMSO) : δ 13.0-12.4 (br, 1H), 11.05 (s, 1H), 9.59 (s, 2H), 9.35 (s, 2H), 9.32 (s, 2H), 8.41 (d, J = 1.5 Hz, 1H), 8.12 (d, J = 9.0 Hz, 1H), 8.06 (dd, J = 7.8, 1.5 Hz, 1H), 7.69 (d, J = 8.4 Hz, 1H), 7.33 (d, J = 7.8 Hz, 1H), 7.18 (d, J = 8.4 Hz, 1H), 4.11 (s, 3H), 3.93 (dt, J = 3.3, 9.0 Hz, 1H), 3.75-3.60 (m, 1H), 3.65-3.30 (m, 2H), 2.30 (s, 3H), 0.92 (s, 9H).

Example 47(26)

2-[2-(4-amidinophenylcarbamoyl)-6-propoxy-3-pyridyl]-6-[(1(S)-hydroxymethyl-2, 2-dimethylpropyl)carbamoyl]benzoic acid methanesulfonate

[0872]



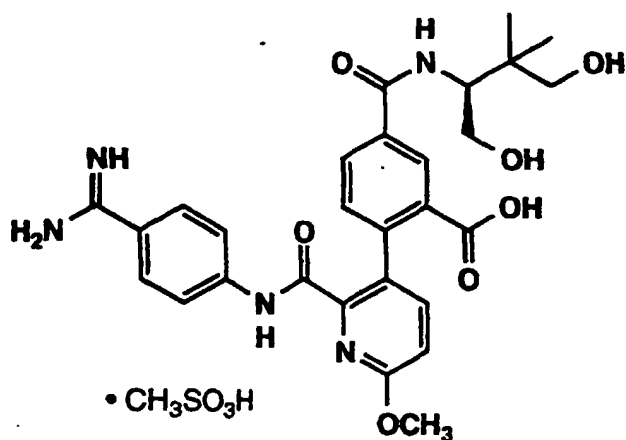
TLC : Rf 0.20 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d_6 -DMSO) : δ 10.6 (s, 1H), 9.19 (br s, 2H), 8.86 (br s, 2H), 8.40 (d, J = 1.5 Hz, 1H), 8.11 (d, J = 9.3 Hz, 1H), 8.03 (dd, J = 8.1, 1.5 Hz, 1H), 7.89 (d, J = 9.0 Hz, 2H), 7.77 (d, J = 9.0 Hz, 2H), 7.63 (d, J = 8.7 Hz, 1H), 7.29 (d, J = 8.1 Hz, 1H), 7.10 (d, J = 8.7 Hz, 1H), 4.46 (t, J = 6.6 Hz, 2H), 3.93 (dt, J = 3.3, 9.3 Hz, 1H), 3.68 (dd, J = 11.1, 3.3 Hz, 1H), 3.51 (dd, J = 11.1, 9.3 Hz, 1H), 2.31 (s, 3H), 1.81 (sextet, J = 6.6 Hz, 2H), 1.04 (t, J = 6.6 Hz, 3H), 0.92 (s, 9H).

Example 47(27)

2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-[(1(S), 2-bishydroxy methyl-2-methylpropyl)carbamoyl]benzoic acid methanesulfonate

[0873]



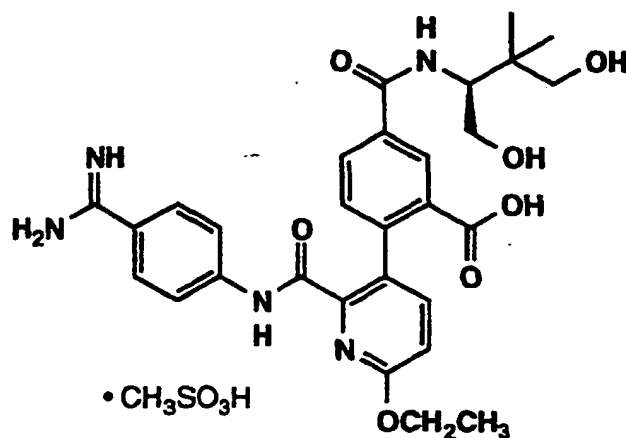
TLC : R_f 0.60 (Ethyl acetate : Acetic acid : Water = 3 : 1 : 0.5) ;

NMR (d₆-DMSO) : δ 12.71 (br.s, 1H), 10.61 (s, 1H), 9.18 (s, 2H), 8.82 (s, 2H), 8.41 (d, J = 1.8 Hz, 1H), 8.23 (d, J = 8.7 Hz, 1H), 8.03 (dd, J = 8.1, 1.8 Hz, 1H), 7.90 (d, J = 9.0 Hz, 2H), 7.78 (d, J = 9.0 Hz, 2H), 7.65 (d, J = 8.7 Hz, 1H), 7.31 (d, J = 8.1 Hz, 1H), 7.13 (d, J = 8.7 Hz, 1H), 4.10 (s, 3H), 4.01 (m, 1H), 3.70 (dd, J = 10.8, 3.3 Hz, 1H), 3.57 (dd, J = 10.8, 9.0 Hz, 1H), 3.80-3.20 (br, 2H), 3.27 (d, J = 10.8 Hz, 1H), 3.11 (d, J = 10.8 Hz, 1H), 2.31 (s, 3H), 0.92 (s, 3H), 0.83 (s, 3H).

Example 47(28)

2-[2-(4-amidinophenylcarbamoyl)-6-ethoxy-3-pyridyl]-5-[(1(S), 2-bishydroxy methyl-2-methylpropyl)carbamoyl]benzoic acid methanesulfonate

[0874]



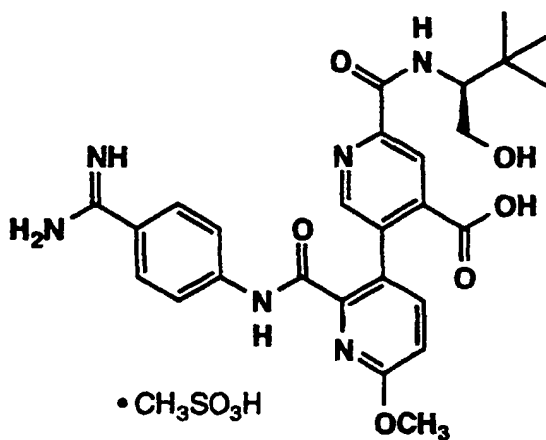
TLC : R_f 0.60 (Ethyl acetate : Acetic acid : Water = 3 : 1 : 0.5) ;

NMR (d₆-DMSO) : δ 12.72 (br, 1H), 10.57 (s, 1H), 9.19 (s, 2H), 8.84 (s, 2H), 8.40 (d, J = 1.8 Hz, 1H), 8.23 (d, J = 9.0 Hz, 1H), 8.02 (dd, J = 8.1, 1.8 Hz, 1H), 7.89 (d, J = 9.0 Hz, 2H), 7.77 (d, J = 9.0 Hz, 2H), 7.64 (d, J = 8.4 Hz, 1H), 7.31 (d, J = 8.1 Hz, 1H), 7.10 (d, J = 8.4 Hz, 1H), 4.56 (q, J = 6.9 Hz, 2H), 4.01 (d, J = 3.6, 9.0 Hz, 1H), 3.69 (dd, J = 11.0, 3.6 Hz, 1H), 3.57 (dd, J = 11.0, 9.0 Hz, 1H), 3.80-3.20 (br, 2H), 3.27 (d, J = 11.0 Hz, 1H), 3.11 (d, J = 11.0 Hz, 1H), 2.30 (s, 3H), 1.41 (t, J = 6.9 Hz, 3H), 0.92 (s, 3H), 0.82 (s, 3H).

Example 47(29)

5-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-2-[(1(S)-hydroxymethyl-2, 2-dimethylpropyl)carbamoyl]-4-pyridinecarboxylic acid methanesulfonate

[0875]



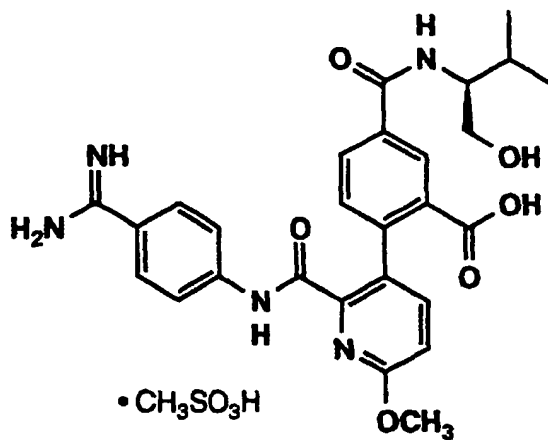
TLC : R_f 0.26 (Chloroform : Methanol : Water = 7 : 3 : 0.3) ;

NMR (300 MHz, DMSO-d₆) : δ 13.47 (br.s, 1H), 10.66 (s, 1H), 9.24 (s, 2H), 8.99 (s, 2H), 8.58 (s, 1H), 8.41 (s, 1H), 8.32 (d, J = 10.0 Hz, 1H), 7.91 (d, J = 9.0 Hz, 2H), 7.81-7.78 (m, 3H), 7.20 (d, J = 8.8 Hz, 1H), 4.12 (s, 3H), 3.86 (m, 1H), 3.63-3.60 (m, 2H), 2.32 (s, 3H), 0.94 (s, 9H).

Example 47(30)

2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-[(1(S)-hydroxymethyl-2-methylpropyl)carbamoyl]benzoic acid
methanesulfonate

[0876]



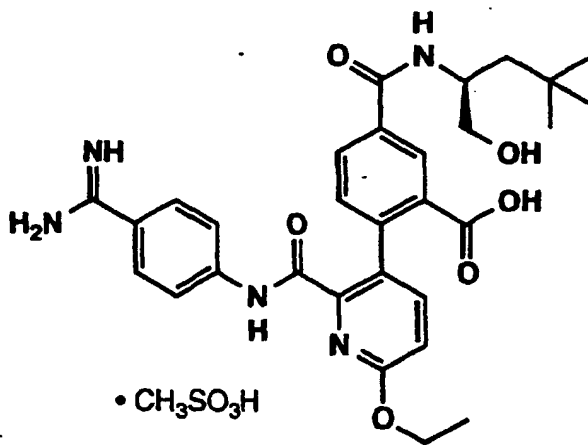
TLC : R_f 0.09 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (300 MHz, d₆-DMSO) : δ 12.8-12.5 (broad, 1H), 10.61 (s, 1H), 9.17 (brs, 2H), 8.81 (brs, 2H), 8.42 (d, J = 2.0 Hz, 1H), 8.21 (brd, J = 9.0 Hz, 1H), 8.04 (dd, J = 8.0, 2.0 Hz, 1H), 7.90 (d, J = 8.7 Hz, 2H), 7.77 (d, J = 8.7 Hz, 2H), 7.65 (d, J = 8.4 Hz, 1H), 7.29 (d, J = 8.0 Hz, 1H), 7.12 (d, J = 8.4 Hz, 1H), 4.09 (s, 3H), 3.90-3.80 (m, 1H), 3.58-3.47 (m, 2H), 2.32 (s, 3H), 1.99-1.87 (m, 1H), 0.92 (d, J = 6.9 Hz, 3H), 0.90 (d, J = 6.9 Hz, 3H).

Example 47(31)

2-[2-(4-amidinophenylcarbamoyl)-6-ethoxy-3-pyridyl]-5-[(1(S)-hydroxymethyl-3,3-dimethylbutyl)carbamoyl]benzoic acid
methanesulfonate

[0877]



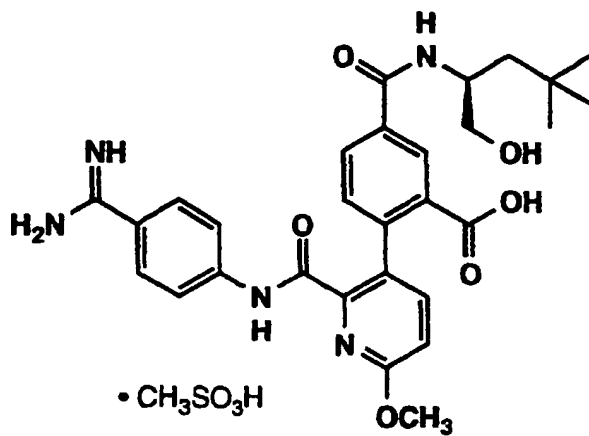
TLC : Rf 0.35 (Chloroform : Methanol : Water = 7 : 3 : 0.3) ;

NMR (300 MHz, DMSO-d₆) : δ 12.68 (br.s, 1H), 10.57 (s 1H), 9.19 (s, 2H), 8.85 (s, 2H), 8.39 (d, J = 2.0 Hz, 1H),
 8.28 (br.d, J = 9.0 Hz, 1H), 8.00 (dd, J = 8.0, 2.0 Hz, 1H), 7.89 (d, J = 9.0 Hz, 2H), 7.77 (d, J = 9.0 Hz, 2H), 7.63 (d,
 J = 8.0 Hz, 1H), 7.28 (d, J = 8.0 Hz, 1H), 7.09 (d, J = 8.0 Hz, 1H), 4.55 (q, J = 7.0 Hz, 2H), 4.12 (m, 1H), 3.41-3.22
 (m, 3H), 2.31 (s, 3H), 1.52 (d, J = 5.4 Hz, 2H), 1.41 (t, J = 7.0 Hz, 3H), 0.91 (s, 9H).

Example 47(32)

2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-[(1(S)-hydroxymethyl-3, 3-dimethylbutyl)carbamoyl]benzoic
 acid methanesulfonate

[0878]



TLC : Rf 0.50 (Chloroform : Methanol : Water = 7 : 3 : 0.3) ;

NMR (300 MHz, DMSO-d₆) : δ 12.68 (br.s, 1H), 10.57 (s 1H), 9.19 (s, 2H), 8.85 (s, 2H), 8.39 (d, J = 2.0 Hz, 1H),
 8.28 (br.d, J = 9.0 Hz, 1H), 8.00 (dd, J = 8.0, 2.0 Hz, 1H), 7.89 (d, J = 9.0 Hz, 2H), 7.77 (d, J = 9.0 Hz, 2H), 7.63 (d,
 J = 8.0 Hz, 1H), 7.28 (d, J = 8.0 Hz, 1H), 7.09 (d, J = 8.0 Hz, 1H), 4.55 (q, J = 7.0 Hz, 2H), 4.12 (m, 1H), 3.41-3.22
 (m, 3H), 2.31 (s, 3H), 1.52 (d, J = 5.4 Hz, 2H), 1.41 (t, J = 7.0 Hz, 3H), 0.91 (s, 9H).

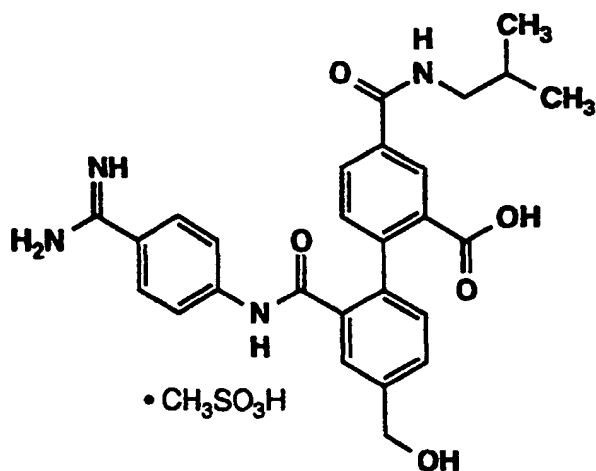
Example 48(1) — 48(3)

[0879] The following compounds were obtained by the same procedure as a series of reaction of Reference Exam-
 ple 26 → Example 45 → Example 11, using a corresponding compound.

Example 48(1)

2'-(4-amidinophenylcarbamoyl)-4'-hydroxymethyl-4-(2-methylpropylcarbamoyl)-2-biphenylcarboxylic acid methanesulfonate

[0880]



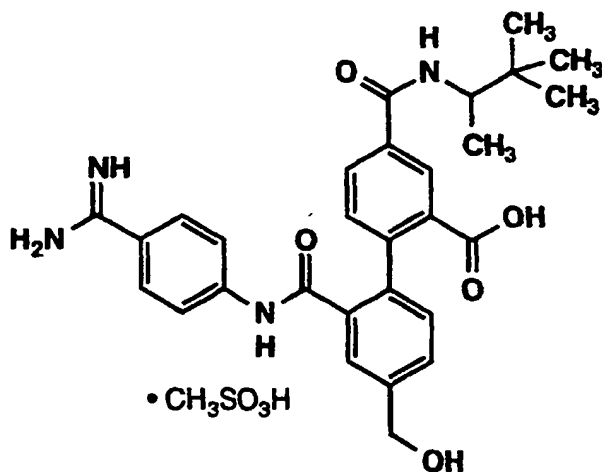
TLC : R_f 0.50 (Chloroform : Methanol : Water = 7 : 3 : 0.3) ;

NMR (d₆-DMSO) : δ 10.53 (s, 1H), 9.13 (s, 2H), 8.75 (s, 2H), 8.64 (br.t, J = 6.3 Hz, 1H), 8.30 (d, J = 2.0 Hz, 1H), 7.95 (dd, J = 8.0, 2.0 Hz, 1H), 7.72 (s, 4H), 7.62 (s, 1H), 7.51 (d, J = 8.0 Hz, 1H), 7.31 (d, J = 8.0 Hz, 1H), 7.23 (d, J = 8.0 Hz, 1H), 4.65 (s, 2H), 3.09 (t, J = 6.3 Hz, 2H), 2.32 (s, 3H), 1.85 (m, 1H), 0.89 (d, J = 6.6 Hz, 6H).

Example 48(2)

2'-[4-(amidinophenylcarbamoyl)-4'-hydroxymethyl-4-(1, 2, 2-trimethylpropyl carbamoyl)-2-biphenylcarboxylic acid methanesulfonate

[0881]



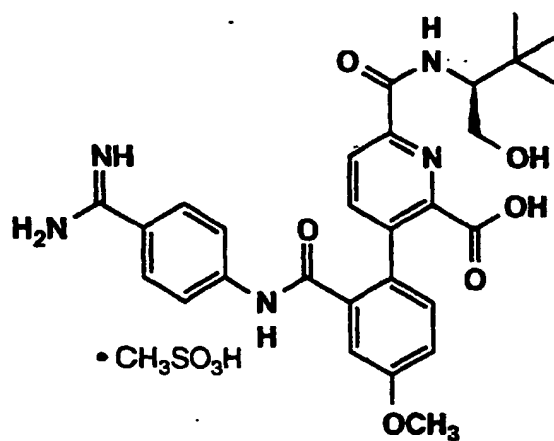
TLC : Rf 0.18 (Chloroform : Methanol : Water = 8 : 2 : 0.2) ;

NMR (d_6 -DMSO) : δ 10.57 (s, 1H), 9.13 (s, 2H), 8.79 (s, 2H), 8.26 (d, J = 2.0 Hz, 1H), 8.17 (d, J = 6.3 Hz, 1H), 7.93 (dd, J = 8.0, 2.0 Hz, 1H), 7.73 (s, 4H), 7.63 (s, 1H), 7.51 (d, J = 8.0 Hz, 1H), 7.29 (d, J = 8.0 Hz, 1H), 7.22 (d, J = 8.0 Hz, 1H), 5.42 (br.s, 1H), 4.65 (s, 2H), 3.99 (m, 1H), 2.33 (s, 3H), 1.08 (d, J = 6.6 Hz, 3H), 0.90 (s, 9H).

Example 48(3)

3-[2-(4-amidinophenylcarbamoyl)-4-methoxyphenyl]-6-[(1(S)-hydroxymethyl-2, 2-dimethylpropyl)carbamoyl]-2-pyridinecarboxylic acid methanesulfonate

[0882]



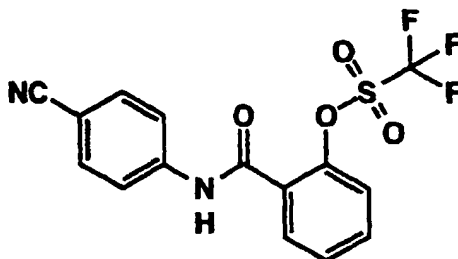
TLC : Rf 0.27 (Chloroform : Methanol : Water = 8 : 2 : 0.2) ;

NMR (d_6 -DMSO) : δ 13.04 (br.s, 1H), 10.82 (br.s 1H), 9.14 (s, 2H), 8.81 (s, 2H), 8.48 (br.d, J = 10.2 Hz, 1H), 8.16 (d, J = 8.0 Hz, 1H), 7.89 (d, J = 8.0 Hz, 1H), 7.75 (s, 4H), 7.33-7.17 (m, 3H), 4.62 (br.s, 1H), 3.90 (s, 3H), 3.85-3.40 (m, 3H), 2.31 (s, 3H), 0.92 (s, 9H).

Reference Example 27

4-[(2-trifluoromethylsulfonyloxyphenyl)carbonylamino]phenylnitrile

[0883]



[0884] Trifluoromethanesulfonic acid anhydrous (0.75 ml) was dropped into a solution of 2-(4-cyanophenyl)carbonylphenol (885 mg) in pyridine (5 ml) at 0 °C. The mixture was stirred for 1 hour at 0 °C. The reaction mixture was diluted with water, and extracted with ethyl acetate. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried over anhydrous sodium sulfate and concentrated. The residue was purified by column chromatography on silica gel (hexane : ethyl acetate = 2 : 1 \rightarrow 1 : 1) to give the present compound (1.25 g) having the following physical data.

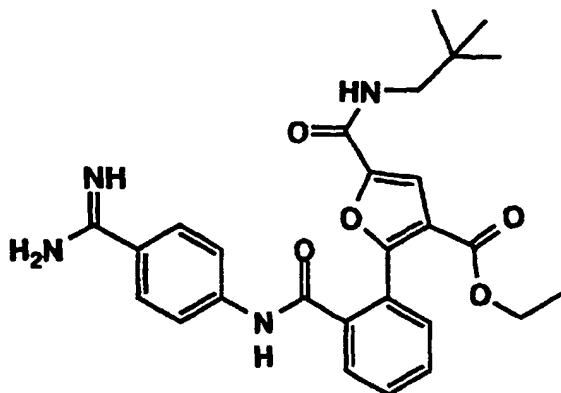
TLC : Rf 0.20 (Hexane : Ethyl acetate = 2 : 1) ;

NMR(200 MHz, $CDCl_3$) : δ 8.09 (br.s, 1H), 7.92 (dd, J = 8.0, 1.5 Hz, 1H), 7.78 (d, J = 8.8 Hz, 2H), 7.67 (d, J = 8.8 Hz, 2H), 7.70-7.60 (m, 1H), 7.56 (dt, J = 1.5, 8.0 Hz, 1H), 7.42 (dd, J = 8.0, 1.5 Hz, 1H).

Example 49

Ethyl 2-[2-(4-amidinophenylcarbamoyl)phenyl]-5-(2, 2-dimethylpropyl carbamoyl)-3-furancarboxylate

[0885]



The title compound having the following physical data was obtained by the same procedure as a series of reaction of Example 37, using 4-[2-[5-(2, 2-dimethylpropylcarbamoyl)-3-ethoxycarbonyl-2-furyl]phenylcarbamoyl]phenylmethylthioimide which was obtained by the same procedure as a series of reaction of Reference Example 4 → Reference Example 8 → Reference Example 5 → Reference Example 3 → Reference Example 20, using a compound prepared in Reference Example 27.

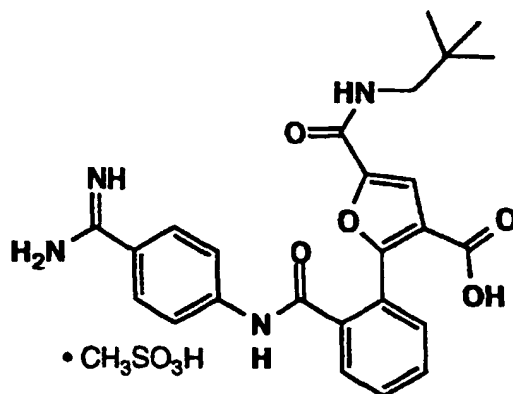
TLC : Rf 0.63 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (300 MHz, d_6 -DMSO) : δ 11.0-10.4 (br, 1H), 10.4-9.6 (br, 3H), 8.19 (t, J = 6.6 Hz, 1H), 7.85-7.75 (m, 2H), 7.75 (like s, 4H), 7.7-7.65 (m, 2H), 7.51 (s, 1H), 4.06 (q, J = 7.0 Hz, 2H), 2.99 (d, J = 6.6 Hz, 2H), 1.10 (t, J = 7.0 Hz, 3H), 0.82 (s, 9H).

Example 50

2-[2-(4-amidinophenylcarbamoyl)phenyl]-5-(2, 2-dimethylpropylcarbamoyl)-3-furancarboxylic acid methanesulfonate

[0887]



[0888] The title compound having the following physical data was obtained by the same procedure as a series of reaction of Example 11, using a compound prepared in Example 49.

5 TLC : Rf 0.31 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;
 NMR (d_6 -DMSO) : δ 12.9-12.6 (br, 1H), 10.80 (s, 1H), 9.17 (s, 2H), 8.85 (s, 2H), 8.15 (t, J = 6.6 Hz, 1H), 7.82 (d, J = 9.0 Hz, 2H), 7.77 (d, J = 9.0 Hz, 2H), 7.8-7.7 (m, 2H), 7.7-7.6 (m, 2H), 7.45 (s, 1H), 2.99 (d, J = 6.6 Hz, 2H), 2.33 (s, 3H), 0.81 (s, 9H).

10 Example 51

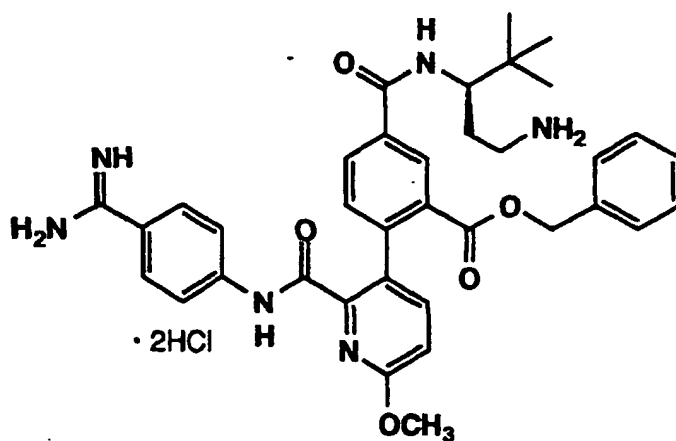
Benzyl 2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-[(3-amino-1(S)-t-butylpropyl)carbamoyl]benzoate dihydrochloride

15 [0889]

20

25

30



35

[0890] The title compound having the following physical data was obtained by the same procedure as a series of reaction of Example 1 → Reference Example 8, using 3-[4-(3-t-butylcarbonylamino-1(R)-t-butylpropylcarbamoyl)-2-benzyloxycarbonylphenyl]-6-methoxy-2-pyridinecarboxylic acid which was prepared by the same procedure as a series of reaction of Reference Example 1 → Reference Example 2 → Reference Example 3 → Reference Example 4 → Reference Example 5 using a corresponding compound. TLC : Rf 0.10 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) .

45

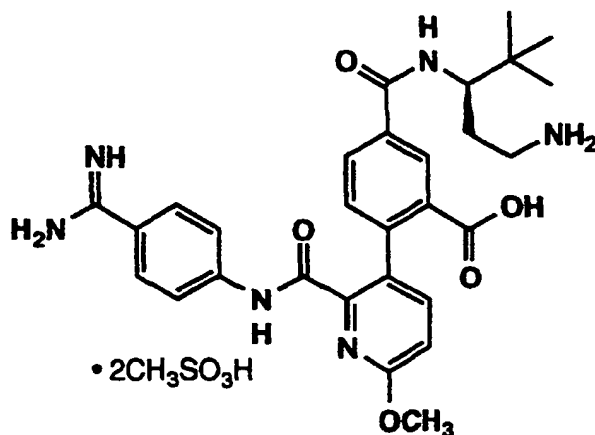
50

55

Example 52

2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-[(3-amino-1(S)-t-butylpropyl)carbamoyl]benzoic acid dimethanesulfonate

[0891]



[0892] The title compound having the following physical data was obtained by the same procedure as a series of reaction of Example 2, using a compound prepared in Example 51.

TLC : Rf 0.60 (Ethyl acetate : Acetic acid : Water = 3 : 1 : 1) ;

NMR (d_6 -DMSO) : δ 12.75 (br, 1H), 10.63 (s, 1H), 9.19 (s, 2H), 8.84 (s, 2H), 8.41 (d, J = 1.8 Hz, 1H), 8.28 (d, J = 9.9 Hz, 1H), 8.04 (dd, J = 8.1, 1.8 Hz, 1H), 7.92 (d, J = 9.3 Hz, 2H), 7.79 (d, J = 9.3 Hz, 2H), 7.71 (br, 2H), 7.64 (d, J = 8.7 Hz, 1H), 7.33 (d, J = 8.1 Hz, 1H), 7.15 (d, J = 8.7 Hz, 1H), 4.11 (s, 3H), 3.96 (m, 1H), 2.85-2.70 (m, 2H), 2.32 (s, 6H), 1.91 (m, 1H), 1.77 (m, 1H), 0.96 (s, 9H).

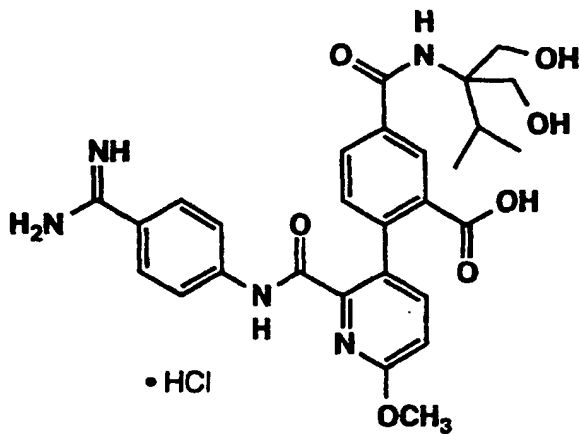
Example 53(1) — 53(8)

[0893] The following compounds were obtained by the same procedure as a series of reaction of Reference Example 8 → Example 52 (without a procedure of conversion to methanesulfoxide thereof), using a compound prepared in Example 40(51), or were obtained by the same procedure as a series of reaction of Example 51 → Example 52 using a corresponding compound.

Example 53(1)

2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-[(1, 1-bishydroxy methyl-2-methylpropyl)carbamoyl]benzoic acid hydrochloride

[0894]



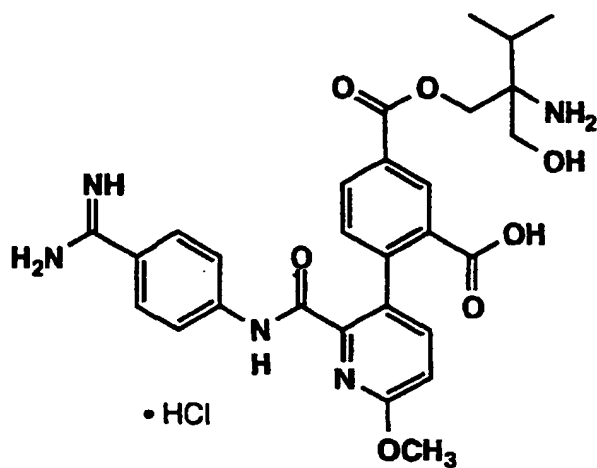
TLC : Rf 0.50 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d₆-DMSO) : δ 12.0-11.4 (br, 1H), 9.23 (s, 2H), 9.11 (s, 2H), 8.18 (s, 1H), 7.84-7.71 (m, 6H), 7.61 (s, 1H), 7.53 (d, J = 8.1 Hz, 1H), 7.17 (d, J = 7.8 Hz, 1H), 7.03 (d, J = 8.4 Hz, 1H), 4.94 (d, J = 5.4 Hz, 1H), 4.92 (d, J = 5.4 Hz, 1H), 4.02 (s, 3H), 3.74 (dd, J = 11.4, 5.4 Hz, 2H), 3.65 (dd, J = 11.4, 5.4 Hz, 2H), 2.41 (m, 1H), 0.93 (d, J = 6.9 Hz, 6H).

Example 53(2)

2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-[(2-amino-2-hydroxymethyl-3-methylbutyl)carbamoyl]benzoic acid hydrochloride

[0895]



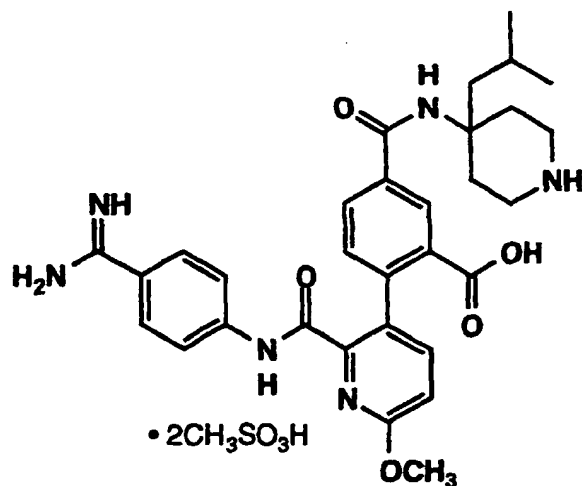
TLC : Rf 0.20 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1);

NMR (d_6 -DMSO) : δ 12.9-12.5 (br, 1H), 9.36 (s, 2H), 9.26 (s, 2H), 8.60-7.90 (br, 2H), 8.28 (s, 1H), 8.07 (d, J = 8.4 Hz, 1H), 7.77 (d, J = 8.7 Hz, 2H), 7.68 (d, J = 8.7 Hz, 2H), 7.49 (d, J = 8.4 Hz, 1H), 7.17 (d, J = 7.8 Hz, 1H), 6.99 (d, J = 8.4 Hz, 1H), 5.55 (br, 1H), 4.37 (s, 2H), 3.97 (s, 3H), 3.64 (s, 2H), 2.18 (dd, J = 7.2, 6.6 Hz, 1H), 0.98 (d, J = 6.6 Hz, 3H), 0.96 (d, J = 6.6 Hz, 3H).

Example 53(3)

2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-[(4-(2-methylpropyl)-4-piperidino)carbamoyl]benzoic acid dimethanesulfonate

[0896]



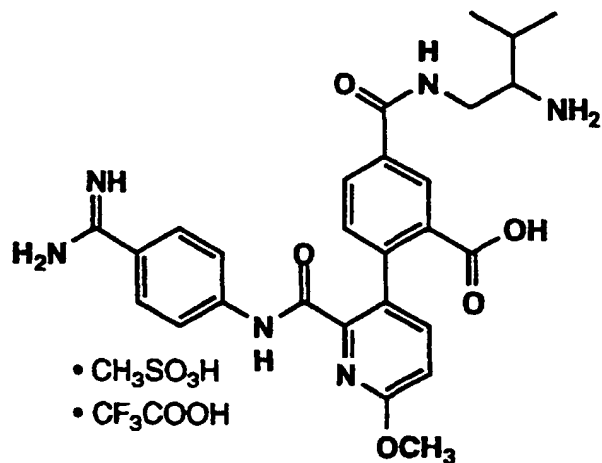
TLC : Rf 0.70 (Ethyl acetate : Acetic acid : Water = 3 : 1 : 1) ;

NMR (d₆-DMSO) : δ 10.6 (s, 1H), 9.19 (br s, 2H), 8.89 (br s, 2H), 8.43 (br s, 2H), 8.36 (d, J = 2.1 Hz, 1H), 8.06 (s, 1H), 8.02 (dd, J = 8.1, 2.1 Hz, 1H), 7.90 (d, J = 9.3 Hz, 2H), 7.79 (d, J = 9.3 Hz, 1H), 7.63 (d, J = 8.7 Hz, 1H), 7.30 (d, J = 8.7 Hz, 1H), 7.13 (d, J = 8.7 Hz, 1H), 4.10 (s, 3H), 3.20-3.16 (m, 2H), 3.06-3.02 (m, 2H), 2.64-2.59 (m, 2H), 2.33 (s, 6H), 1.80-1.55 (m, 1H), 1.74 (s, 2H), 1.66-1.59 (m, 2H), 0.90 (d, J = 6.0 Hz, 6H).

Example 53(4)

2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-[(2-amino-3-methyl butyl)carbamoyl]benzoic acid methanesulfonate trifluoroacetate

[0897]



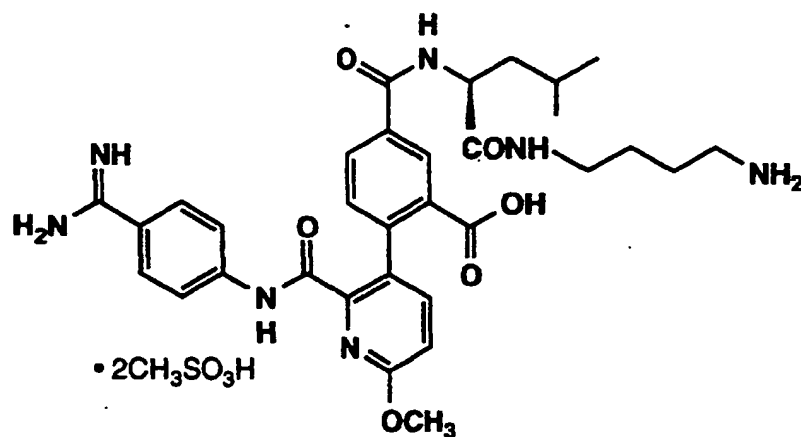
TLC : R_f 0.50 (Ethyl acetate : Acetic acid : Water = 3 : 3 : 1) ;

NMR (d₆-DMSO) : δ 12.8-12.5 (br, 1H), 10.61 (s, 1H), 9.21 (s, 2H), 9.02 (s, 2H), 8.84 (t, J = 5.7 Hz, 1H), 8.44 (d, J = 1.8 Hz, 1H), 8.07 (dd, J = 8.1, 1.8 Hz, 1H), 7.93 (brd, J = 3.6 Hz, 2H), 7.91 (d, J = 9.0 Hz, 2H), 7.79 (d, J = 9.0 Hz, 2H), 7.64 (d, J = 8.4 Hz, 1H), 7.33 (d, J = 8.1 Hz, 1H), 7.12 (d, J = 8.4 Hz, 1H), 4.10 (s, 3H), 3.5-3.3 (m, 3H), 3.08 (m, 1H), 2.34 (s, 3H), 1.96 (m, 1H), 1.01 (d, J = 6.6 Hz, 3H), 0.99 (d J = 6.6 Hz, 3H).

Example 53(5)

2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-[(1(S)-(4-aminobutyl carbamoyl)-3-methylbutyl)carbamoyl]benzoic acid dimethanesulfonate

[0898]



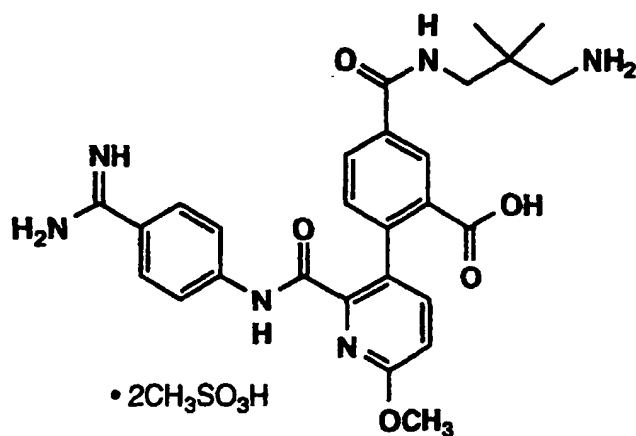
TLC : Rf 0.66 (Ethyl acetate : Acetic acid : Water = 3 : 1 : 1) ;

NMR (d_6 -DMSO) : δ 12.75 (br, 1H), 10.62 (s, 1H), 9.21 (s, 2H), 8.89 (s, 2H), 8.70 (d, J = 8.4 Hz, 1H), 8.47 (d, J = 1.8 Hz, 1H), 8.10 (dd, J = 8.1, 1.8 Hz, 1H), 8.06 (t, J = 5.7 Hz, 1H), 7.91 (d, J = 9.3 Hz, 2H), 7.80 (d, J = 9.3 Hz, 2H), 7.72 (br, 2H), 7.65 (d, J = 8.4 Hz, 1H), 7.32 (d, J = 8.1 Hz, 1H), 7.14 (d, J = 8.4 Hz, 1H), 4.52 (m, 1H), 4.12 (s, 3H), 3.14-3.04 (m, 2H), 2.86-2.76 (m, 2H), 2.34 (s, 6H), 1.80-1.62 (m, 2H), 1.60-1.42 (m, 5H), 0.93 (d, J = 6.3 Hz, 3H), 0.90 (d, J = 6.3 Hz, 3H).

Example 53(6)

2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-[(3-amino-2,2-dimethylpropyl)carbamoyl]benzoic acid
dimethanesulfonate

[0899]



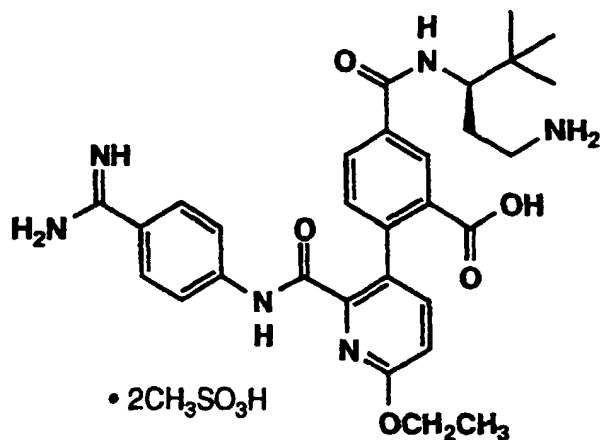
TLC : R_f 0.34 (Ethyl acetate : Acetic acid : Water = 3 : 1 : 1) ;

NMR (d₆-DMSO) : δ 10.62 (s, 1H), 9.19 (s, 2H), 9.00 (t, J = 6.3 Hz, 1H), 8.81 (s, 2H), 8.48 (d, J = 1.5 Hz, 1H), 8.08 (dd, J = 7.2, 1.5 Hz, 1H), 7.91 (d, J = 9.0 Hz, 2H), 7.84-7.72 (m, 3H), 7.79 (d, J = 9.0 Hz, 2H), 7.64 (d, J = 8.4 Hz, 1H), 7.35 (d, J = 7.2 Hz, 1H), 7.14 (d, J = 8.4 Hz, 1H), 4.12 (s, 3H), 3.26 (d, J = 6.3 Hz, 2H), 2.70-2.62 (m, 2H), 2.32 (s, 6H), 1.00 (s, 6H).

Example 53(7)

2-[2-(4-amidinophenylcarbamoyl)-6-ethoxy-3-pyridyl]-5-[(3-amino-1(S)-t-butylpropyl)carbamoyl]benzoic acid dimethanesulfonate

[0900]



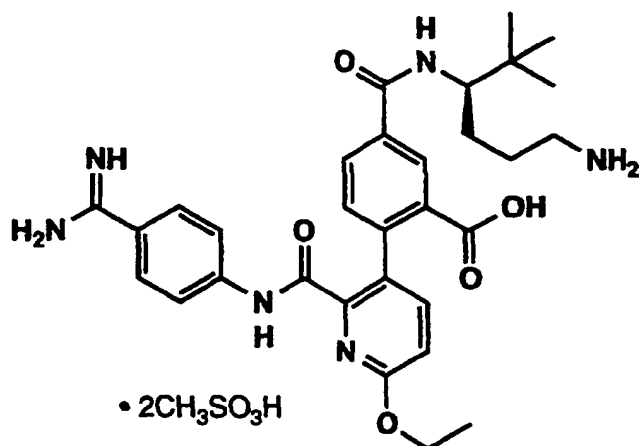
TLC : R_f 0.60 (Ethyl acetate : Acetic acid : Water = 3 : 3 : 1) ;

NMR (d₆-DMSO) : δ 12.8-12.3 (brd, 1H), 10.58 (s, 1H), 9.20 (s, 2H), 8.90 (s, 2H), 8.39 (d, J = 1.8 Hz, 1H), 8.27 (d, J = 9.9 Hz, 1H), 8.02 (dd, J = 8.1, 1.8 Hz, 1H), 7.88 (d, J = 9.0 Hz, 2H), 7.78 (d, J = 9.0 Hz, 2H), 7.77 (s, 2H), 7.62 (d, J = 8.4 Hz, 1H), 7.31 (d, J = 8.1 Hz, 1H), 7.10 (d, J = 8.4 Hz, 1H), 4.56 (dd, J = 12.9, 6.0 Hz, 2H), 3.94 (t, J = 10.2 Hz, 1H), 2.78 (m, 2H), 2.32 (s, 6H), 1.90 (m, 1H), 1.76 (m, 1H), 1.41 (t, J = 6.0 Hz, 3H), 0.95 (s, 9H).

Example 53(8)

2-[2-(4-amidinophenylcarbamoyl)-6-ethoxy-3-pyridyl]-5-[(4-amino-1(S)-t-butylbutyl)carbamoyl]benzoic acid dimethanesulfonate

[0901]



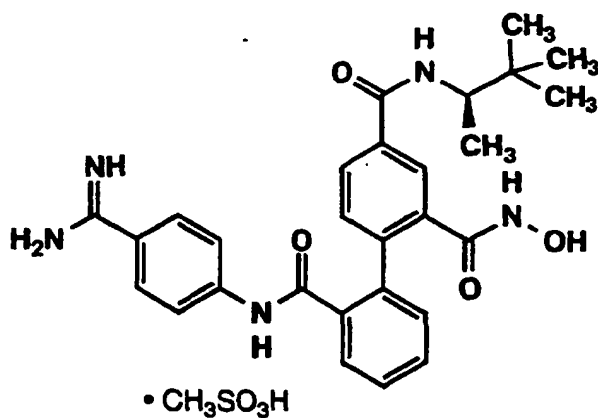
TLC : R_f 0.60 (Ethyl acetate : Acetic acid : Water = 3 : 3 : 1) ;

NMR (300 MHz, d₆-DMSO) : δ 12.8-12.3 (brd, 1H), 10.58 (s, 1H), 9.20 (s, 2H), 8.88 (s, 2H), 8.41 (d, J = 1.8 Hz, 1H), 8.16 (d, J = 9.6 Hz, 1H), 8.04 (dd, J = 7.8, 1.8 Hz, 1H), 7.88 (d, J = 9.0 Hz, 2H), 7.79 (d, J = 9.0 Hz, 2H), 7.68 (brd, 2H), 7.61 (d, J = 8.4 Hz, 1H), 7.30 (d, J = 8.4 Hz, 1H), 7.10 (d, J = 7.8 Hz, 1H), 4.56 (m, 2H), 3.83 (m, 1H), 2.80-2.70 (m, 2H), 2.31 (s, 6H), 1.68-1.40 (m, 4H), 1.41 (t, J = 6.9 Hz, 3H), 0.93 (s, 9H).

Example 54

N-hydroxy-2'-[(4-amidinophenylcarbamoyl)-4-[(1(R), 2, 2-trimethylpropyl) carbamoyl]-2-biphenylcarboxamide methanesulfonate

[0902]



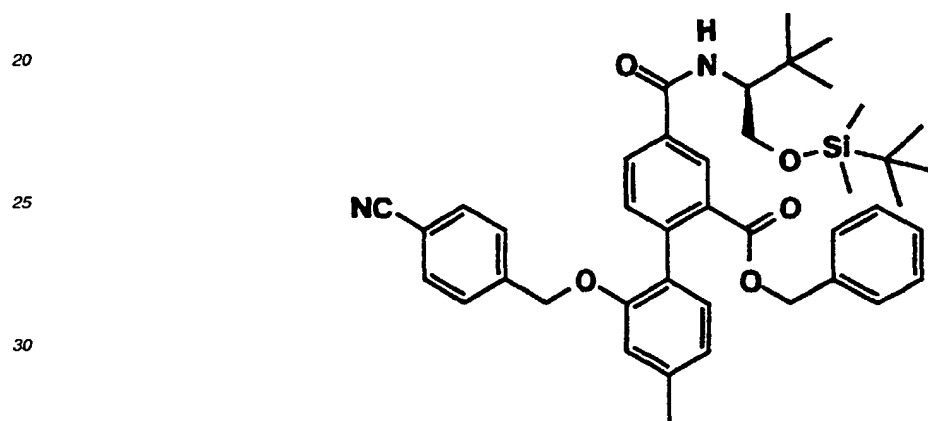
[0903] The title compound having the following physical data was obtained by the same procedure as a series of reaction of Example 21 → Example 22, using a salt-free compound of a compound prepared in Example 41(12).

5 TLC : Rf 0.36 (Chloroform : Methanol : Water = 7 : 3 : 0.3) ;
 NMR (d_6 -DMSO) : δ 11.52 (br, 1H), 11.22 (s, 1H), 9.15 (s, 2H), 8.91 (s, 2H), 8.11 (d, J = 9.6 Hz, 1H), 8.02 (d, J = 1.5 Hz, 1H), 7.89 (dd, J = 7.8, 1.5 Hz, 1H), 7.73-7.68, (m, 3H), 7.60-7.54 (m, 4H), 7.22 (d, J = 7.8 Hz, 1H), 7.12 (m, 1H), 3.96 (m, 1H), 2.38 (s, 3H), 1.07 (d, J = 6.6 Hz, 3H), 0.89 (s, 9H).

10 Reference Example 28

Benzyl 2'-(4-nitrilebenzyloxy)-4'-methyl-4-[(1(S)-t-butyl(dimethylsilyloxymethyl)-2, 2-dimethylpropyl)carboxamide]-2-biphenylcarboxylate

15 **[0904]**



35

[0905] To a solution of a compound (1.10 g) prepared by the same procedure as a series of reaction of Reference Example 4 using 2-(4-formylbenzyloxy)-4-methylphenylboric acid and benzyl 2-trifluoromethylsulfonyloxy-5-((1(S)-t-butyl(dimethylsilyloxymethyl)-2, 2-dimethylpropyl)carbamoyl)benzoate, in pyridine (20 ml), hydroxylamine hydrochloride (220 mg) and anhydrous acetic acid (0.75 ml) was added. The mixture was stirred for 1.5 hour at 90 °C. The reaction mixture was diluted with ethyl acetate. The solution was washed two times with a saturated aqueous solution of sodium chloride. The organic layer was dried over anhydrous sodium sulfate and concentrated. The residue was purified by column chromatography on silica gel (hexane : ethyl acetate = 3 : 1) to give the title compound (1.05 g) having the following physical data.

45

 TLC : Rf 0.69 (Hexane : Ethyl acetate = 3 : 1) ;
 NMR (200 MHz, $CDCl_3$) : δ 8.31 (d, J = 1.8 Hz, 1H), 7.98 (dd, J = 8.0, 1.8 Hz, 1H), 7.50 (d, J = 8.4 Hz, 2H), 7.42 (d, J = 8.0 Hz, 1H), 7.3-7.2 (m, 3H), 7.20 (d, J = 8.4 Hz, 2H), 7.16 (d, J = 8.0 Hz, 1H), 7.1-7.0 (m, 2H), 6.90 (br.d, J = 8.0 Hz, 1H), 6.7-6.5 (m, 1H), 6.60 (br.s, 1H), 5.06 (s, 2H), 4.83 (s, 2H), 4.04 (m, 1H), 3.83 (dd, J = 10.6, 3.4 Hz, 1H), 3.76 (dd, J = 10.6, 4.0 Hz, 1H), 2.37 (s, 3H), 1.04 (s, 9H), 0.88 (s, 9H), 0.06 (s, 3H), 0.03 (s, 3H).

50

Example 55(1) — 55(3)

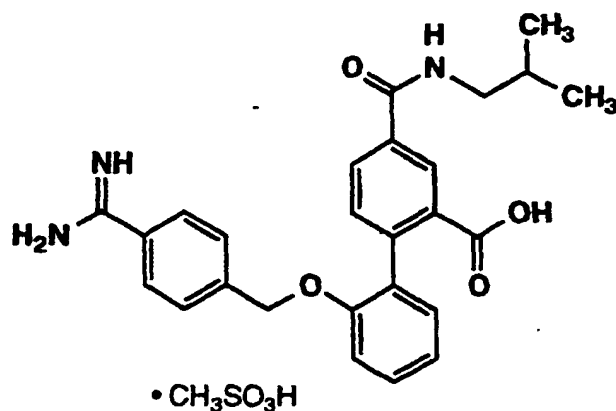
[0906] The following compounds were obtained by the same procedure as a series of reaction of Reference Example 20 → Example 37 → Example 45 → Example 38 using a compound prepared in Reference Example 28, or were obtained by the same procedure as a series of reaction of Reference Example 4 → Reference Example 28 → Reference Example 20 → Example 37 → Example 38 using a corresponding compounds.

55

Example 55(1)

2'-(4-amidinobenzyloxy)-4-(2-methylpropylcarbamoyl)-2-biphenylcarboxylic acid methanesulfonate

[0907]

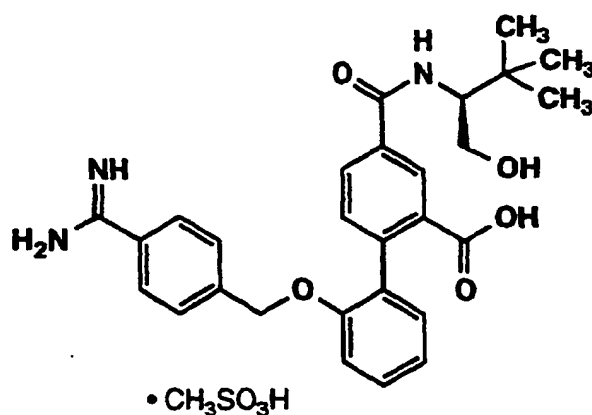
TLC : R_f 0.29 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d₆-DMSO) : δ 12.70 (1H, br.s), 9.24 (2H, br.s), 8.81 (2H, br.s), 8.66 (1H, br.t, J = 6.0 Hz), 8.29 (1H, br.s), 8.03 (1H, br.d, J = 7.0 Hz), 7.72 (2H, d, J = 8.1 Hz), 7.47 (2H, d, J = 8.1 Hz), 7.40 (1H, d, J = 7.8 Hz), 7.32 (1H, br.t, J = 7.8 Hz), 7.21 (1H, br.d, J = 7.8 Hz), 7.1-7.0 (2H, m), 5.15 (2H, s), 3.10 (2H, t, J = 6.0 Hz), 2.30 (3H, s), 1.85 (1H, like septet, J = 6.0 Hz), 0.89 (6H, d, J = 6.0 Hz).

Example 55(2)

2'-(4-amidinobenzyloxy)-4-(1(S)-hydroxymethyl-2, 2-dimethylpropylcarbamoyl)-2-biphenylcarboxylic acid methanesulfonate

[0908]



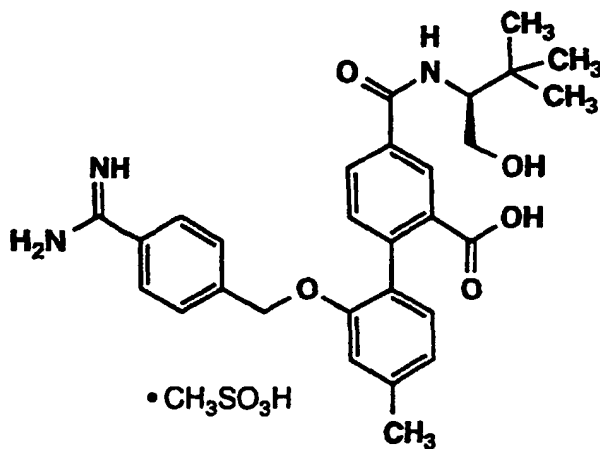
TLC : Rf 0.29 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d_6 -DMSO) : δ 9.27 (s, 2H), 8.99 (s, 2H), 8.29 (d, J = 1.5 Hz, 1H), 8.09 (d, J = 9.3 Hz, 1H), 8.05 (dd, J = 1.5, 8.1 Hz, 1H), 7.73 (d, J = 8.0 Hz, 2H), 7.48 (d, J = 8.0 Hz, 2H), 7.39 (d, J = 8.1 Hz, 1H), 7.32 (dt, J = 1.5, 7.5 Hz, 1H), 7.20 (dd, J = 1.5, 7.5 Hz, 1H), 7.1-7.0 (m, 2H), 5.16 (s, 2H), 4.1-3.6 (m, 2H), 3.92 (dt, J = 3.3, 9.3 Hz, 1H), 3.67 (dd, J = 3.3, 11.4 Hz, 1H), 3.49 (dd, J = 9.3, 11.4 Hz, 1H), 2.34 (s, 3H), 0.92 (s, 9H).

Example 55(3)

2'-(4-amidinobenzyloxy)-4'-methyl-4-(1(S)-hydroxymethyl-2, 2-dimethylpropyl carbamoyl)-2-biphenylcarboxylic acid
methanesulfonate

[0909]



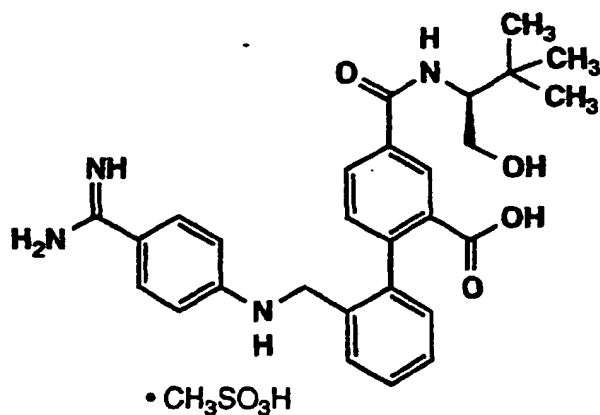
TLC : Rf 0.70 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR (d_6 -DMSO) : δ 9.27 (s, 2H), 8.96 (s, 2H), 8.27 (d, J = 1.8 Hz, 1H), 8.07 (d, J = 9.3 Hz, 1H), 8.03 (dd, J = 8.1, 1.8 Hz, 1H), 7.73 (d, J = 8.4 Hz, 2H), 7.48 (d, J = 8.4 Hz, 2H), 7.36 (d, J = 8.1 Hz, 1H), 7.08 (d, J = 7.5 Hz, 1H), 6.93 (s, 1H), 6.86 (d, J = 7.5 Hz, 1H), 5.14 (s, 2H), 3.91 (m, 1H), 4.0-3.6 (br, 2H), 3.67 (dd, J = 11.4, 3.6 Hz, 1H), 3.48 (dd, J = 11.4, 9.0 Hz, 1H), 2.33 (s, 3H), 2.33 (s, 3H), 0.91 (s, 9H).

Example 56

2'-(4-amidinophenylaminomethyl)-4-(1(S)-hydroxymethyl-2, 2-dimethylpropyl carbamoyl)-2-biphenylcarboxylic acid
methanesulfonate

[0910]



[0911] The title compound having the following physical data was obtained by the same procedure as a series of reaction of Reference Example 15 → Reference Example 16 → Example 16 → Example 45 → Example 2, using benzyl 2'-formyl-4-(1(R)-t-butylidimethylsilyloxymethyl-2, 2-dimethylpropyl carbamoyl)-2-biphenylcarboxylate which was obtained by the same procedure as a series of reaction of Reference Example 4 using a corresponding compound.

TLC : R_f 0.54 (Ethyl acetate : Acetic acid : Water = 3 : 1 : 1) ;

NMR (d₆-DMSO) : δ 8.74 (2H, br s), 8.36 (1H, d, J = 1.4 Hz), 8.31 (2H, br s), 8.12 (1H, d, J = 9.2 Hz), 8.07-8.04 (1H, m), 7.52 (2H, d, J = 8.8 Hz), 7.44 (1H, d, J = 8.0 Hz), 7.30-7.26 (4H, m), 7.12-7.06 (1H, m), 6.55 (2H, d, J = 8.8 Hz), 4.07 (2H, br s), 3.98-3.86 (1H, m), 3.67 (1H, dd, J = 4.0, 11.2 Hz), 3.55-3.30 (2H, m), 2.30 (3H, s), 0.91 (9H, s).

Reference Example 29

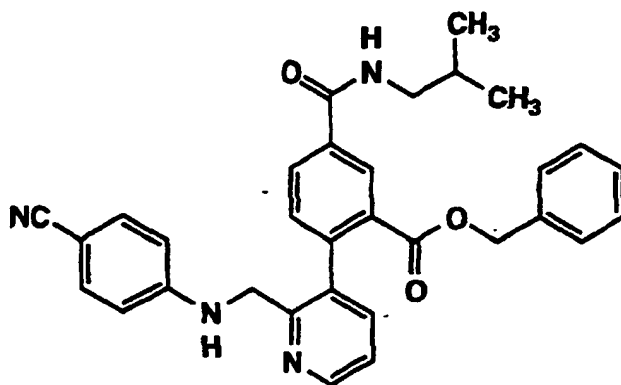
Benzyl 2-[2-(4-cyanophenylaminomethyl)-3-pyridyl]-5-(2-methylpropyl carbamoyl)benzoate

5 [0912]

10

15

20



25

30

[0913] Benzyl 2-(2-formyl-3-pyridyl)-5-(2-methylpropylcarbamoyl)benzoate (674 mg) which was obtained by the same procedure as a series of reaction of Reference Example 4 using a corresponding compound, and 4-cyanoaniline (382 mg) were dissolved into ethanol (3 ml) and acetic acid (3 ml). Sodium cyanoborohydride (153 mg) was slowly added to the mixture at 0 °C. The mixture was stirred for 30 minutes, and was made to more pH 8 by adding 1N aqueous solution of sodium hydroxide. A saturated aqueous solution of sodium bicarbonate was added to the solution. The solution was extracted with ethyl acetate. The organic layer was washed with a saturated aqueous solution of sodium bicarbonate and a saturated aqueous solution of sodium chloride, successively, dried over anhydrous magnesium sulfate and concentrated. The residue was purified by column chromatography on silica gel (hexane : ethyl acetate = 2 : 1 → 1 : 1) to give the title compound (692 mg) having the following physical data.

35

40

TLC : Rf 0.21 (Hexane : Ethyl acetate = 1 : 1) ;

NMR(CDCl₃) : δ 8.55 (d, J = 1.8 Hz, 1H), 8.44 (d, J = 1.8 Hz, 1H), 8.05 (dd, J = 8.1, 1.8 Hz, 1H), 7.40 (dd, J = 7.8, 1.8 Hz, 1H), 7.4-7.3 (m, 3H), 7.3-7.2 (m, 4H), 7.1-7.0 (m, 2H), 6.43 (d, J = 8.7 Hz, 2H), 6.30 (br.t, J = 6.6 Hz, 1H), 5.80 (br.t, J = 4.5 Hz, 1H), 5.03 (s, 2H), 4.04 (dd, J = 15.6, 4.5 Hz, 1H), 3.95 (dd, J = 15.6, 3.9 Hz, 1H), 3.35 (t, J = 6.6 Hz, 2H), 1.95 (like septet, J = 6.6 Hz, 1H), 1.02 (d, J = 6.6 Hz, 3H), 1.02 (d, J = 6.6 Hz, 3H).

45

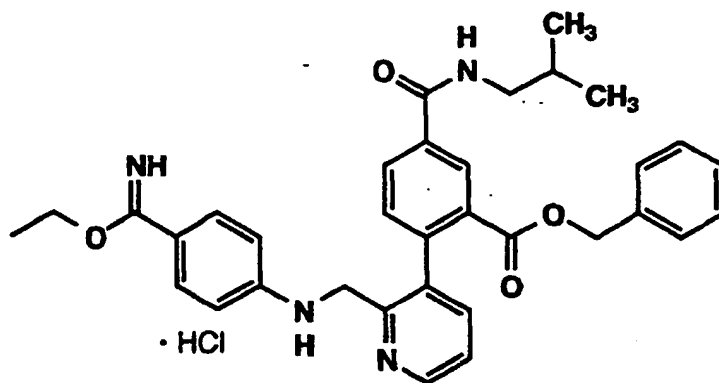
50

55

Reference Example 30

Benzyl 2-[2-(4-(imino-ethoxymethyl)phenylaminomethyl)-3-pyridyl]-5-(2-methyl propylcarbamoyl)benzoate hydrochloride

[0914]

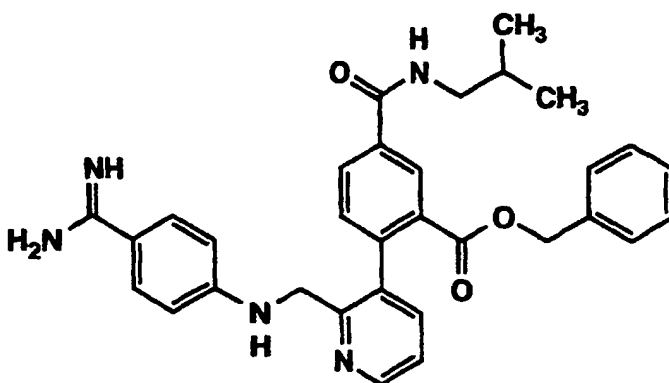


[0915] The compound prepared in Reference Example 29 (681 mg) was dissolved into ethanol (7 ml) and methylene chloride (7 ml), and the mixture was stirred at -20 °C. Chloride gas was blown into the mixture slowly for 1 hour to be the solution was under 18 °C. The solution was sealed up, and allowed to stand for 27 hours at 5 °C. The reaction mixture was concentrated to give the title compound (643 mg) having the following physical data. TLC: R_f 0.61 (Chloroform : Methanol : Water = 9 : 1 : 0.1).

Example 57

Benzyl 2-[2-(4-amidinophenylaminomethyl)-3-pyridyl]-5-(2-methylpropyl carbamoyl)benzoate

[0916]



[0917] The compound prepared in Reference Example 30 (643 mg) was dissolved into ethanol (25 ml), and the solution was stirred at 0 °C. An ammonium gas was blown into the mixture slowly for 15 minutes to be the solution was under 20 °C. The solution was sealed up, and allowed to stand for 28 hours at room temperature. The reaction mixture

was concentrated. The residue was purified by column chromatography on silica gel (Chloroform : Methanol = 10 : 1 → Chloroform : Methanol : Water = 10 : 2 : 0.1) to give the title compound (307 mg) having the following physical data.

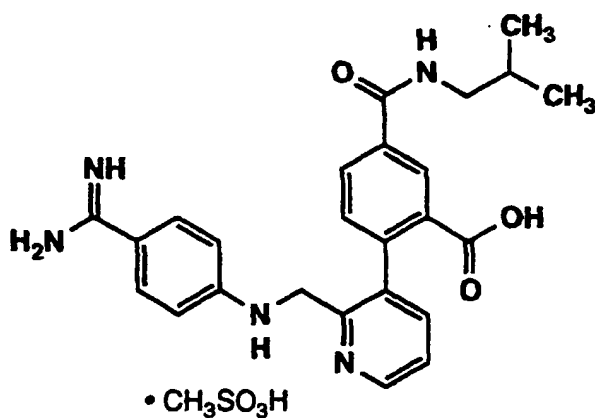
TLC : Rf 0.68 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR(d_6 -DMSO) : δ 8.77 (t, J = 6.0 Hz, 1H), 8.9-8.4 (br, 3H), 8.52 (dd, J = 4.8, 1.5 Hz, 1H), 8.47 (d, J = 1.8 Hz, 1H), 8.13 (dd, J = 7.8, 1.8 Hz, 1H), 7.53 (d, J = 9.0 Hz, 2H), 7.6-7.45 (m, 1H), 7.46 (d, J = 7.8 Hz, 1H), 7.35-7.25 (m, 4H), 7.2-7.1 (m, 2H), 6.98 (t, J = 5.4 Hz, 1H), 6.53 (d, J = 9.0 Hz, 2H), 5.07 (d, J = 14.4 Hz, 1H), 5.04 (d, J = 14.4 Hz, 1H), 4.2-4.0 (m, 2H), 3.11 (t, J = 6.0 Hz, 2H), 1.87 (like septet, J = 6.6 Hz, 1H), 0.90 (d, J = 6.6 Hz, 3H), 0.90 (d, J = 6.6 Hz, 3H).

Example 58

2-[2-(4-amidinophenylaminomethyl)-3-pyridyl]-5-(2-methylpropylcarbamoyl) benzoic acid methanesulfonate

[0918]



[0919] The title compound was obtained by the same procedure as a series of reaction of Example 2, using a compound prepared in Example 57.

TLC : Rf 0.26 (Chloroform : Methanol : Acetic acid = 10 : 2 : 1) ;

NMR(d_6 -DMSO) : δ 8.81 (br.s, 2H), 8.77 (t, J = 6.0 Hz, 1H), 8.64 (dd, J = 5.1, 1.2 Hz, 1H), 8.51 (d, J = 1.8 Hz, 1H), 8.49 (br.s, 2H), 8.13 (dd, J = 8.0, 1.8 Hz, 1H), 7.87 (br.d, 1H), 7.62 (br.t, 1H), 7.55 (d, J = 9.0 Hz, 2H), 7.51 (d, J = 8.0 Hz, 1H), 6.58 (d, J = 9.0 Hz, 2H), 4.32 (d, J = 16.5 Hz, 1H), 4.22 (d, J = 16.5 Hz, 1H), 4.4-3.5 (br, 2H), 3.12 (t, J = 6.6 Hz, 2H), 2.33 (s, 3H), 1.87 (like septet, J = 6.6 Hz, 1H), 0.90 (d, J = 6.6 Hz, 3H), 0.90 (d, J = 6.6 Hz, 3H).

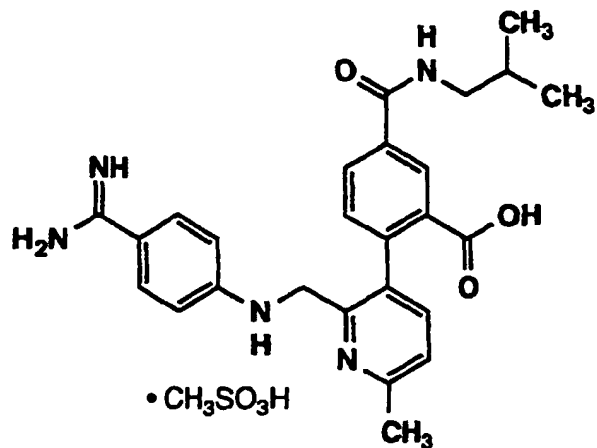
Example 59(1) — 59(2)

[0920] The following compounds were obtained by the same procedure as a series of reaction of Reference Example 29 → Reference Example 30 → Example 57 → Example 58, using a corresponding compound.

Example 59(1)

2-[2-(4-amidinophenylaminomethyl)-6-methyl-3-pyridyl]-5-(2-methylpropyl carbamoyl)benzoic acid methanesulfonate

[0921]

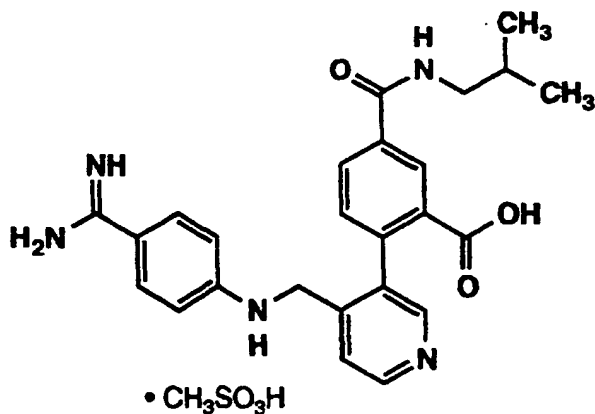
TLC : R_f 0.58 (Chloroform : Methanol : Water = 7 : 3 : 0.3) ;

NMR (d₆-DMSO) : δ 8.81 (brs, 2H), 8.56 (brt, J = 6.0 Hz, 1H), 8.54 (brs, 2H), 8.50 (d, J = 1.5 Hz, 1H), 8.10 (dd, J = 8.0, 1.5 Hz, 1H), 7.96 (brd, J = 7.5 Hz, 1H), 7.64 (brd, J = 7.5 Hz, 1H), 7.54 (d, J = 9.0 Hz, 2H), 7.45 (d, J = 8.0 Hz, 1H), 6.51 (d, J = 9.0 Hz, 2H), 4.34 (brs, 2H), 3.11 (brt, J = 6.0 Hz, 2H), 2.72 (s, 3H), 2.35 (s, 3H), 1.93-1.79 (m, 1H), 0.89 (d, J = 6.6 Hz, 6H).

Example 59(2)

2-[4-(4-amidinophenylaminomethyl)-3-pyridyl]-5-(2-methylpropylcarbamoyl) benzoic acid methanesulfonate

[0922]



TLC : Rf 0.36 (Chloroform : Methanol : Water = 7 : 3 : 0.3) ;

NMR (d₆-DMSO) : δ 8.88 (brs, 2H), 8.83 (brt, J = 6.0 Hz, 1H), 8.78 (d, J = 5.7 Hz, 1H), 8.71 (s, 1H), 8.63 (brs, 2H), 8.59 (d, J = 1.8 Hz, 1H), 8.22 (dd, J = 8.0, 1.8 Hz, 1H), 7.72 (d, J = 5.7 Hz, 1H), 7.63 (d, J = 8.0 Hz, 1H), 7.59 (d, J = 9.0 Hz, 2H), 6.58 (d, J = 9.0 Hz, 2H), 4.32 (brd, J = 18 Hz, 1H), 4.14 (brd, J = 18 Hz, 1H), 3.13 (brt, J = 6.0 Hz, 2H), 2.35 (s, 3H), 1.95-1.81 (m, 1H), 0.90 (d, J = 6.6 Hz, 6H).

Formulation example 1

[0923] The following components were admixed in conventional method and punched out to obtain 100 tablets each containing 100 mg of active ingredient.

• 2-[2-(4-aminophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-[[1(S)-hydroxy methyl-2, 2-dimethylpropyl]carbamoyl]benzoic acid methanesulfonate	10.0g
• Carboxymethyl Cellulose calcium (disintegrating agent)	0.2g
• Magnesium stearate (lubricating agent)	0.1g
• Microcrystalline cellulose	9.7g

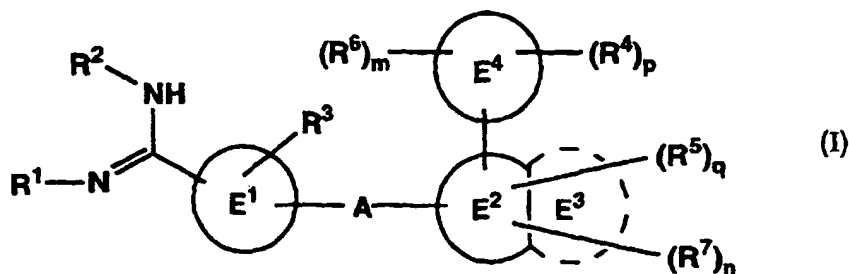
Formulation example 2

[0924] The following components were admixed in conventional method. The solution was sterilized in conventional manner, placed 5 ml portions into ampoules and freeze-dried to obtain 100 ampoules each containing 20 mg of the active ingredient.

• 2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-[(1(S)-hydroxy methyl-2, 2-dimethylpropyl)carbamoyl]benzoic acid methanesulfonate	2.0g
• mannitol	5.0g
• distilled water	1000 ml

Claims

1. Amidino derivatives of the formula (I) :



wherein R¹ and R² each independently, is

- 1) hydrogen,
- 2) hydroxy,

- 3) C1-4 alkoxy carbonyl,
 4) C2-4 alkenyloxy carbonyl,
 5) C1-4 alkoxy carbonyloxy or
 6) -COO-(C1-4 alkyl)-phenyl,
 with the proviso that when R¹ is group excepting hydrogen, R² is hydrogen, or when R² is group excepting hydrogen, R¹ is hydrogen ;

R³ is

- 1) hydrogen,
 2) C1-4 alkyl,
 3) hydroxy,
 4) -O-(C1-4 alkyl)-phenyl, or
 5) halogen atom ;

E¹ ring is

- 1) 5-7 membered unsaturated carbocyclic ring or
 2) 5-7 membered unsaturated heterocyclic ring ;

E² ring is

- 1) 5-7 membered unsaturated carbocyclic ring or
 2) 5-7 membered unsaturated heterocyclic ring ;

E³ ring is

- 1) absent,
 2) 5-7 membered unsaturated or saturated carbocyclic ring or
 3) 5-7 membered unsaturated or saturated heterocyclic ring ;

E⁴ ring is

- 1) 5-6 membered unsaturated carbocyclic ring or
 2) 5-6 membered unsaturated heterocyclic ring ;

R⁴ and R⁵ each independently, is

- 1) -COOR⁸, in which R⁸ is hydrogen, C1-8 alkyl, -(C1-4 alkyl)-phenyl or -(C1-4 alkyl)-O-(C1-4 alkyl) ;
 2) -(C1-4 alkyl)-COOR⁹, in which R⁹ is hydrogen, C1-8 alkyl, -(C1-4 alkyl)-phenyl or -(C1-4 alkyl)-O-(C1-4 alkyl) ;
 3) -(C2-4 alkenyl)-COOR¹⁰, in which R¹⁰ is hydrogen, C1-8 alkyl, -(C1-4 alkyl)-phenyl or -(C1-4 alkyl)-O-(C1-4 alkyl) ;
 4) -O-(C1-4 alkyl)-COOR¹¹, in which R¹¹ is hydrogen, C1-8 alkyl, -(C1-4 alkyl)-phenyl or -(C1-4 alkyl)-O-(C1-4 alkyl) ;
 5) -CONR¹²R¹³, in which R¹² is hydrogen, C1-4 alkyl, R¹³ is hydroxy, -O-(C1-4 alkyl)-phenyl or cyano ;
 6) -P(O)(OR¹⁴)₂, in which R¹⁴ is hydrogen, C1-4 alkyl or -(C1-4 alkyl)-phenyl ; or
 7) tetrazol -5-yl which is optionally substituted by C1-8 alkyl ;
 p and q each independently, is 0 or 1-2, with the proviso that p + q is 1 or 2 ;

R⁶ and R⁷ each independently, is

- 1) hydrogen,
 2) C1-8 alkyl,
 3) nitro,
 4) cyano,
 5) halogen atom,
 6) -(C1-4 alkyl)-O-(C1-4 alkyl)-phenyl,

- 7) $-NR^{15}R^{16}$, in which R^{15} and R^{16} each independently, is hydrogen or C1-8 alkyl ;
 8) $-OR^{17}$, in which R^{17} is hydrogen, C1-8 alkyl, CF_3 , C2-5 acyl, $-(C1-4 \text{ alkyl})\text{-phenyl}$, $-(C1-4 \text{ alkyl})\text{-OH}$, $-(C1-4 \text{ alkyl})\text{-O}\text{-}(C1-4 \text{ alkyl})$, or $-(C1-4 \text{ alkyl})\text{-O}\text{-}(C1-4 \text{ alkyl})\text{-O}\text{-}(C1-4 \text{ alkyl})$;
 9) $-(C1-4 \text{ alkyl})\text{-OR}^{17}$, in which R^{17} is as hereinbefore defined ;
 10) $-J^1\text{-}J^2$, in which J^1 is

- (1) $-\text{CONR}^{18}-$, in which R^{18} is hydrogen or C1-4 alkyl ;
 (2) $-\text{NR}^{19}\text{CO}-$, in which R^{19} is hydrogen or C1-4 alkyl ;
 (3) $-\text{SO}_2\text{NR}^{20}-$, in which R^{20} is hydrogen or C1-4 alkyl ;
 (4) $-\text{NR}^{21}\text{SO}_2-$, in which R^{21} is hydrogen or C1-4 alkyl ;
 (5) $-(C1-4 \text{ alkyl})\text{-NR}^{22}-$, in which R^{22} is hydrogen or C1-4 alkyl ;
 (6) $-\text{CO}-$,
 (7) $-(C1-4 \text{ alkyl})\text{-NR}^{23}\text{CO}-$, in which R^{23} is hydrogen or C1-4 alkyl ;

J^2 is

(1) C1-15 alkyl optionally substituted by 1-3 of following groups (i) - (x):

- (i) C3-7 cycloalkyl optionally substituted by $-(C1-4 \text{ alkyl})\text{-OR}^{24}$;
 (ii) phenyl,
 (iii) 5-7 membered saturated heterocyclic ring optionally substituted by carboxyl or C1-4 alkoxy-carbonyl ;
 (iv) OR^{24} , in which R^{24} is hydrogen, C1-4 alkyl, $-\text{COO}\text{-}(C1-4 \text{ alkyl})\text{-phenyl}$, C2-5 acyl, or $-(C1-4 \text{ alkyl})\text{-phenyl}$;
 (v) $\text{NR}^{25}\text{R}^{26}$, in which R^{25} is hydrogen or C1-4 alkyl, R^{26} is hydrogen, C1-4 alkyl, $-\text{COO}(C1-4 \text{ alkyl})\text{-phenyl}$, imino(C1-4 alkyl) or C1-4 alkoxy-carbonyl ;
 (vi) $-\text{S(O)}_r\text{-}(C1-4 \text{ alkyl})$, in which r is 0-2 ;
 (vii) $-\text{COOR}^{27}$, in which R^{27} is hydrogen, C1-4 alkyl or $-(C1-4 \text{ alkyl})\text{-phenyl}$;
 (viii) $-\text{CONR}^{28}\text{R}^{29}$, in which R^{28} and R^{29} each independently, is

(i) hydrogen, (ii) C1-4 alkyl, (iii) hydroxy, or (iv) C1-4 alkyl substituted by one of hydroxy, phenyl or $\text{NR}^{25}\text{R}^{26}$, or R^{28} and R^{29} taken together with the nitrogen atom to which they are attached form 5-6 membered saturated heterocyclic ring containing nitrogen atom ;

- (ix) halogen atom,
 (x) trihalomethyl ;

- (2) C2-8 alkenyl,
 (3) C5-7 cycloalkyl optionally substituted by 1-3 of C1-4 alkyl, $-\text{COOR}^{27}$, in which R^{27} is as hereinbefore defined; $-(C1-4 \text{ alkyl})\text{-OR}^{24}$, in which R^{24} is as hereinbefore defined;
 (4) $-\text{NR}^{25}\text{R}^{26}$, in which R^{25} and R^{26} is as hereinbefore defined;
 (5) 5-6 membered saturated heterocyclic ring optionally substituted by 1-3 of C1-4 alkyl, oxo, imino(C1-4 alkyl) ;
 or R^{18} and J^2 taken together with the nitrogen atom to which they are attached form saturated heterocyclic ring optionally substituted by 1-3 of C1-8 alkyl, C2-8 alkenyl or $-\text{COOR}^{27}$, in which R^{27} is as hereinbefore defined;

m is 1-3;

n is 1-3;

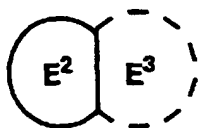
two R^6 taken together with the neighboring two carbon of E^4 ring to which they are attached form 5-6 membered unsaturated carbocyclic ring or 5-6 membered saturated heterocyclic ring, that rings may be substituted by 1-3 of R^4 or R^6 ;

A is

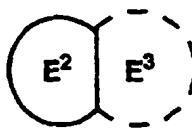
- 1) ethylene,
 2) vinylene,
 3) ethynylene,
 4) $-\text{O-CH}_2-$,

- 5) $-\text{CH}_2-\text{O}-$,
 6) $-\text{NR}^{30}\text{CO}-$, in which R^{30} is hydrogen or C1-4 alkyl ;
 7) $-\text{NR}^{31}\text{CHR}^{32}-$, in which R^{31} is hydrogen or C1-4 alkyl, R^{32} is hydrogen, cyano, COOR^{36} , in which R^{36} is hydrogen or C1-4 alkyl; or $\text{CONR}^{37}\text{R}^{38}$, in which R^{37} and R^{38} each independently, is hydrogen or C1-4 alkyl ;
 8) $-\text{CH}_2-\text{NR}^{33}-$, in which R^{33} is hydrogen or C1-4 alkyl ;
 9) $-\text{S}-\text{CH}_2-$,
 10) $-\text{CH}_2-\text{S}-$,
 11) $-\text{SO}_2\text{NR}^{34}-$, in which R^{34} is hydrogen or C1-4 alkyl ;
 12) $-\text{NR}^{35}\text{SO}_2-$, in which R^{35} is hydrogen or C1-4 alkyl ;
 non-toxic salts thereof, or hydrates thereof.

2. The compound according to claim 1, wherein E^3 ring is absent in the formula:

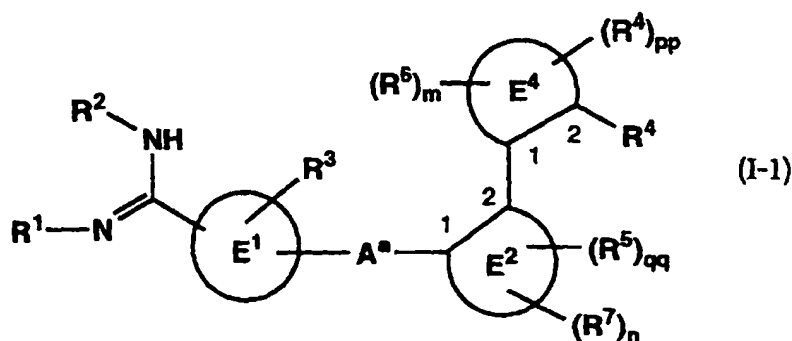


3. The compound according to claim 1, wherein E^3 ring is 5-7 membered unsaturated or saturated carbocyclic ring or 5-7 membered unsaturated or saturated heterocyclic ring in the formula:



4. The compound according to claim 1, wherein A is $-\text{CH}_2-\text{O}-$, $-\text{NR}^{30}\text{CO}-$ or $-\text{NR}^{31}\text{CHR}^{32}-$.

5. Amidino derivatives according to claim 1 of the formula (I-1):



wherein R¹ and R² each independently, is

- 1) hydrogen,
 - 2) hydroxy,
 - 3) C1-4 alkoxy carbonyl,
 - 4) C2-4 alkenyloxy carbonyl,
 - 5) C1-4 alkoxy carbonyloxy or
 - 6) -COO-(C1-4 alkyl)-phenyl,
- with the proviso that when R¹ is group excepting hydrogen, R² is hydrogen, or when R² is group excepting hydrogen, R¹ is hydrogen ;

R³ is

- 1) hydrogen,
- 2) C1-4 alkyl,
- 3) hydroxy,
- 4) -O-(C1-4 alkyl)-phenyl, or
- 5) halogen atom ;

E¹ ring is

- 1) 5-7 membered unsaturated carbocyclic ring or
- 2) 5-7 membered unsaturated heterocyclic ring ;

E² ring is

- 1) 5-7 membered unsaturated carbocyclic ring or
- 2) 5-7 membered unsaturated heterocyclic ring ;

E⁴ ring is

- 1) 5-6 membered unsaturated carbocyclic ring or
- 2) 5-6 membered unsaturated heterocyclic ring ;

R⁴ and R⁵ each independently, is

- 1) -COOR⁸, in which R⁸ is hydrogen, C1-8 alkyl, -(C1-4 alkyl)-phenyl or -(C1-4 alkyl)-O-(C1-4 alkyl) ;
 - 2) -(C1-4 alkyl)-COOR⁹, in which R⁹ is hydrogen, C1-8 alkyl, -(C1-4 alkyl)-phenyl or -(C1-4 alkyl)-O-(C1-4 alkyl) ;
 - 3) -(C2-4 alkenyl)-COOR¹⁰, in which R¹⁰ is hydrogen, C1-8 alkyl, -(C1-4 alkyl)-phenyl or -(C1-4 alkyl)-O-(C1-4 alkyl) ;
 - 4) -O-(C1-4 alkyl)-COOR¹¹, in which R¹¹ is hydrogen, C1-8 alkyl, -(C1-4 alkyl)-phenyl or -(C1-4 alkyl)-O-(C1-4 alkyl) ;
 - 5) -CONR¹²R¹³, in which R¹² is hydrogen, C1-4 alkyl, R¹³ is hydroxy, -O-(C1-4 alkyl)-phenyl or cyano ;
 - 6) -P(O)(OR¹⁴)₂, in which R¹⁴ is hydrogen, C1-4 alkyl or -(C1-4 alkyl)-phenyl ; or
 - 7) tetrazol -5-yl which is optionally substituted by C1-8 alkyl ;
- pp and qq each independently, is 0 or 1, with the proviso that pp + qq is 0 or 1 ;

R⁶ and R⁷ each independently, is

- 1) hydrogen,
- 2) C1-8 alkyl,
- 3) nitro,
- 4) cyano,
- 5) halogen atom,
- 6) -(C1-4 alkyl)-O-(C1-4 alkyl)-phenyl,
- 7) -NR¹⁵R¹⁶, in which R¹⁵ and R¹⁶ each independently, is hydrogen or C1-8 alkyl ;
- 8) -OR¹⁷, in which R¹⁷ is hydrogen, C1-8 alkyl, CF₃, C2-5 acyl, -(C1-4 alkyl)-phenyl, -(C1-4 alkyl)-OH, -

(C1-4 alkyl)-O-(C1-4 alkyl), or -(C1-4 alkyl)-O-(C1-4 alkyl)-O-(C1-4 alkyl) ;

9) -(C1-4 alkyl)-OR¹⁷, in which R¹⁷ is as hereinbefore defined ;

10) -J¹-J², in which J¹ is

(1) -CONR¹⁸-, in which R¹⁸ is hydrogen or C1-4 alkyl ;

(2) -NR¹⁹CO-, in which R¹⁹ is hydrogen or C1-4 alkyl ;

(3) -SO₂NR²⁰-, in which R²⁰ is hydrogen or C1-4 alkyl ;

(4) -NR²¹SO₂-, in which R²¹ is hydrogen or C1-4 alkyl ;

(5) -(C1-4 alkyl)-NR²²-, in which R²² is hydrogen or C1-4 alkyl ;

(6) -CO-,

(7) -(C1-4 alkyl)-NR²³CO-, in which R²³ is hydrogen or C1-4 alkyl ;

J² is

(1) C1-15 alkyl optionally substituted by 1-3 of following groups (i) — (x):

(i) C3-7 cycloalkyl optionally substituted by -(C1-4 alkyl)-OR²⁴ ;

(ii) phenyl,

(iii) 5-7 saturated heterocyclic ring optionally substituted by carboxyl or C1-4 alkoxy carbonyl ;

(iv) OR²⁴, in which R²⁴ is hydrogen, C1-4 alkyl, -COO-(C1-4 alkyl)-phenyl, C2-5 acyl, or -(C1-4 alkyl)-phenyl ;

(v) NR²⁵R²⁶, in which R²⁵ is hydrogen or C1-4 alkyl, R²⁶ is hydrogen, C1-4 alkyl, -COO(C1-4 alkyl)-phenyl, imino(C1-4 alkyl) or C1-4 alkoxy carbonyl ;

(vi) -S(O)_r-(C1-4 alkyl), in which r is 0-2 ;

(vii) -COOR²⁷, in which R²⁷ is hydrogen, C1-4 alkyl or -(C1-4 alkyl)-phenyl ;

(viii) -CONR²⁸R²⁹, in which R²⁸ and R²⁹ each independently, is

(i) hydrogen, (ii) C1-4 alkyl, (iii) hydroxy, or (iv) C1-4 alkyl substituted by one of hydroxy, phenyl or NR²⁵R²⁶, or R²⁸ and R²⁹ taken together with the nitrogen atom to which they are attached form 5-6 membered saturated heterocyclic ring containing nitrogen atom ;

(ix) halogen atom,

(x) trihalomethyl ;

(2) C2-8 alkenyl,

(3) C5-7 cycloalkyl optionally substituted by 1-3 of C1-4 alkyl, -COOR²⁷, in which R²⁷ is as hereinbefore defined; -(C1-4 alkyl)-OR²⁴, in which R²⁴ is as hereinbefore defined;

(4) -NR²⁵R²⁶, in which R²⁵ and R²⁶ is as hereinbefore defined;

(5) 5-6 membered saturated heterocyclic ring optionally substituted by 1-3 of C1-4 alkyl, oxo, imino(C1-4 alkyl) ;

or R¹⁸ and J² taken together with the nitrogen atom to which they are attached form saturated heterocyclic ring optionally substituted by 1-3 of C1-8 alkyl, C2-8 alkenyl or -COOR²⁷, in which R²⁷ is as hereinbefore defined;

m is 1-3;

n is 1-3;

two R⁶ taken together with the neighboring two carbon of E⁴ ring to which they are attached form 5-6 membered unsaturated carbocyclic ring or 5-6 membered saturated heterocyclic ring, that rings may be substituted by 1-3 of R⁴ or R⁶ ;

A^a is

1)-CH₂-O-,

6) -NR³⁰CO-,

7) -NR³¹CHR³²-;

with the proviso that A^a and E⁴ ring attach to E² ring at ortho position, E² ring and essential one R⁴ attach to E⁴ ring at ortho position ;

non-toxic salts thereof, or hydrates thereof.

6. The compound according to claim 1, wherein at least one of R⁶ is -J¹-J².

7. The compound according to claim 1, which is selected from

- (1) 2'-(4-amidinophenylcarbamoyl)-4-((2, 2-dimethylpropyl)carbamoyl)-2-biphenylcarboxylic acid,
- (2) 2'-(4-amidinophenylcarbamoyl)-4-dimethylcarbamoyl-2-biphenylcarboxylic acid,
- (3) 2'-(4-amidinophenylcarbamoyl)-4-methylcarbamoyl-2-biphenylcarboxylic acid,
- (4) 2'-(4-amidinophenylcarbamoyl)-4-((carboxymethyl)carbamoyl)-2-biphenylcarboxylic acid,
- (5) 2'-(4-amidinophenylcarbamoyl)-4-((1-carboxy-2-phenylethyl)carbamoyl)-2-biphenylcarboxylic acid,
- (6) 2'-(4-amidinophenylcarbamoyl)-4-benzylcarbamoyl-2-biphenylcarboxylic acid,
- (7) 2'-(4-amidinophenylcarbamoyl)-4-phenylethylcarbamoyl-2-biphenylcarboxylic acid,
- (8) 2'-(4-amidinophenylcarbamoyl)-4-((2-methylpropyl)carbamoyl)-2-biphenylcarboxylic acid,
- (9) 2'-(4-amidinophenylcarbamoyl)-4'-methoxy-4-((1-methoxycarbonyl-2-methylpropyl)carbamoyl)-2-biphenylcarboxylic acid,
- (10) 2'-(4-amidinophenylcarbamoyl)-4'-methoxy-4-((2-methylpropyl)carbamoyl)-2-biphenylcarboxylic acid,
- (11) 2'-(4-amidinophenylcarbamoyl)-4-isopropylcarbamoyl-2-biphenylcarboxylic acid,
- (12) 2'-(4-amidinophenylcarbamoyl)-4-((3-methylbutyl)carbamoyl)-2-biphenylcarboxylic acid,
- (13) 2'-(4-amidinophenylcarbamoyl)-4-ethylcarbamoyl-2-biphenylcarboxylic acid,
- (14) 2'-(4-amidinophenylcarbamoyl)-4-butylcarbamoyl-2-biphenylcarboxylic acid,
- (15) 2'-(4-amidinophenylcarbamoyl)-4'-methyl-4-((2-methylpropyl)carbamoyl)-2-biphenylcarboxylic acid,
- (16) 2'-(4-amidinophenylcarbamoyl)-4-((cyclohexylmethyl)carbamoyl)-2-biphenylcarboxylic acid,
- (17) 2'-(4-amidinophenylcarbamoyl)-4-((5-(1-butoxycarbonylamino)pentyl)carbamoyl)-2-biphenylcarboxylic acid,
- (18) 2'-(4-amidinophenylcarbamoyl)-4-((1-methylpropyl)carbamoyl)-2-biphenylcarboxylic acid,
- (19) 2'-(4-amidinophenylcarbamoyl)-4-((tetrahydropyran-4-ylmethyl)carbamoyl)-2-biphenylcarboxylic acid,
- (20) 2'-(4-amidinophenylcarbamoyl)-4-((2-hydroxypropyl)carbamoyl)-2-biphenylcarboxylic acid,
- (21) 2'-(4-amidino-2-hydroxyphenylcarbamoyl)-4-((2-methylpropyl)carbamoyl)-2-biphenylcarboxylic acid,
- (22) 2'-(4-amidinophenylcarbamoyl)-4-(N-methyl-N-(2-methylpropyl)carbamoyl)-2-biphenylcarboxylic acid,
- (23) 2'-(4-amidinophenylcarbamoyl)-4-((2-methyl-1-(methylaninomethyl)propyl)carbamoyl)-2-biphenylcarboxylic acid,
- (24) 2'-(4-amidinophenylcarbamoyl)-4-((2-hydroxy-2-methylpropyl)carbamoyl)-2-biphenylcarboxylic acid,
- (25) 2'-(4-amidino-2-methylphenylcarbamoyl)-4-((2-methylpropyl)carbamoyl)-2-biphenylcarboxylic acid,
- (26) 2'-(4-amidinophenylcarbamoyl)-4-((cyclopropylmethyl)carbamoyl)-2-biphenylcarboxylic acid,
- (27) 2'-(4-amidinophenylcarbamoyl)-4-((1-methylcarbamoyl-2-methylpropyl)carbamoyl)-2-biphenylcarboxylic acid,
- (28) 2'-(4-amidinophenylcarbamoyl)-4-((cyclopentylmethyl)carbamoyl)-2-biphenylcarboxylic acid,
- (29) 2'-(4-amidinophenylcarbamoyl)-4-((cyclobutylmethyl)carbamoyl)-2-biphenylcarboxylic acid,
- (30) 2'-(4-amidinophenylcarbamoyl)-4-((1-methoxycarbonyl-2-methylpropyl)carbamoyl)-2-biphenylcarboxylic acid,
- (31) 2'-(4-amidinophenylcarbamoyl)-4-((2-methoxycarbonyl)ethyl)carbamoyl)-2-biphenylcarboxylic acid,
- (32) 2'-(4-amidinophenylcarbamoyl)-4-((3-ethoxycarbonylpropyl)carbamoyl)-2-biphenylcarboxylic acid,
- (33) 2'-(4-amidinophenylcarbamoyl)-4-((1-t-butoxycarbonylpiperidin-4-ylmethyl)carbamoyl)-2-biphenylcarboxylic acid,
- (34) 2'-(4-amidinophenylcarbamoyl)-4-((2-methylthioethyl)carbamoyl)-2-biphenylcarboxylic acid,
- (35) 2'-(4-amidinophenylcarbamoyl)-4-((2-methylsulfinylethyl)carbamoyl)-2-biphenylcarboxylic acid,
- (36) 2'-(4-amidinophenylcarbamoyl)-4-((1-dimethylaminomethyl-2-methylpropyl)carbamoyl)-2-biphenylcarboxylic acid,
- (37) 2'-(4-amidinophenylcarbamoyl)-4-((1-(pyrrolidin-1-ylmethyl)-2-methylpropyl)carbamoyl)-2-biphenylcarboxylic acid,
- (38) 2'-(4-amidinophenylcarbamoyl)-4-((1-hydroxymethyl-2-methylpropyl)carbamoyl)-2-biphenylcarboxylic acid,
- (39) 2'-(4-amidinophenylaminomethyl)-4-((2,2-dimethylpropyl)carbamoyl)-2-biphenylcarboxylic acid,
- (40) 2'-(4-amidinophenylaminomethyl)-4'-methoxy-4-((2-methylpropyl)carbamoyl)-2-biphenylcarboxylic acid,
- (41) 2'-(4-amidinophenylaminomethyl)-4-((2-methylpropyl)carbamoyl)-2-biphenylcarboxylic acid,
- (42) 2'-(4-amidinophenylaminomethyl)-4-((2-methylpropyl)carbamoyl)-2-biphenylcarboxylic acid,
- (43) 2'-(4-(N²-hydroxyamidino)phenylaminomethyl)-4-((2-methylpropyl)carbamoyl)-2-biphenylcarboxylic acid,
- (44) 2'-(4-(N²-hydroxyamidino)phenylcarbamoyl)-4-((2-methylpropyl)carbamoyl)-2-biphenylcarboxylic acid,
- (45) 2-(4-(4-amidinophenylcarbamoyl)pyridin-3-yl)-5-((2-methylpropyl)carbamoyl)benzoic acid,

- (46) 2'-(4-amidinophenylcarbamoyl)-4-propylcarbamoyl-2-biphenylcarboxylic acid,
 (47) 2'-(4-amidinophenylcarbamoyl)-4-((3-hydroxy-2, 2-dimethylpropyl)carbamoyl)-2-biphenylcarboxylic acid,
 (48) 2'-(4-amidinophenylcarbamoyl)-4-((1, 2, 2-trimethylpropyl)carbamoyl)-2-biphenylcarboxylic acid,
 (49) 2'-(4-amidinophenylcarbamoyl)-4-pentylcarbamoyl-2-biphenylcarboxylic acid,
 5 (50) 2'-(4-amidinophenylcarbamoyl)-4-hexylcarbamoyl-2-biphenylcarboxylic acid,
 (51) 2'-(4-amidinophenylcarbamoyl)-4-((1, 2-dimethylpropyl)carbamoyl)-2-biphenylcarboxylic acid,
 (52) 2'-(4-amidinophenylcarbamoyl)-4-(((1S)-1-hydroxymethyl-2-methylpropyl)carbamoyl)-2-biphenylcarboxylic acid,
 (53) 2'-(4-amidinophenylcarbamoyl)-4-((3, 3-dimethylbutyl)carbamoyl)-2-biphenylcarboxylic acid,
 10 (54) 2'-(4-amidinophenylcarbamoyl)-4-(((1R)-1-hydroxymethyl-2-methylpropyl)carbamoyl)-2-biphenylcarboxylic acid,
 (55) 2'-(4-amidinophenylcarbamoyl)-4-(((1S)-1-methoxycarbonyl-2-methylpropyl)carbamoyl)-2-biphenylcarboxylic acid,
 (56) 2'-(4-amidinophenylcarbamoyl)-4-(((1R)-1-methoxycarbonyl-2-methylpropyl)carbamoyl)-2-biphenylcarboxylic acid,
 15 (57) 2-(3-(4-amidinophenylcarbamoyl)pyridin-4-yl)-5-((2-methylpropyl)carbamoyl)benzoic acid,
 (58) 2'-(6-amidinopyridin-3-yl)-4-((2-methylpropyl)carbamoyl)-2-biphenylcarboxylic acid,
 (59) 2'-(4-amidinophenylcarbamoyl)-4'-methoxy-4-((1, 2, 2-trimethylpropyl)carbamoyl)-2-biphenylcarboxylic acid;
 20 (60) 2'-(4-amidinophenylcarbamoyl)-4-(((1S)-1-hydroxymethyl-2, 2-dimethylpropyl)carbamoyl)-biphenylcarboxylic acid,
 (61) 2'-(6-amidinopyridin-3-ylcarbamoyl)-2-((1, 2, 2-trimethylpropyl)carbamoyl)-2-biphenylcarboxylic acid,
 (62) 2'-(4-amidinophenylcarbamoyl)-4-((1-carboxy-2-methylpropyl)carbamoyl)-2-biphenylcarboxylic acid,
 (63) 2'-(4-amidinophenylcarbamoyl)-4-((2-carboxyethyl)carbamoyl)-2-biphenylcarboxylic acid,
 25 (64) 2'-(4-amidinophenylcarbamoyl)-4-((3-carboxypropyl)carbamoyl)-2-biphenylcarboxylic acid,
 (65) 2'-(4-amidinophenylcarbamoyl)-4-((5-aminopentyl)carbamoyl)-2-biphenylcarboxylic acid,
 (66) 2'-(4-amidinophenylcarbamoyl)-4-((piperidin-4-ylmethyl)carbamoyl)-2-biphenylcarboxylic acid,
 (67) 2'-(6-amidinopyridin-3-ylcarbamoyl)-4-((2-methylpropyl)carbamoyl)-2-biphenylcarboxylic acid,
 (68) 2'-(6-amidinopyridin-3-ylcarbamoyl)-4'-methoxy-4-((1, 2, 2-trimethylpropyl)carbamoyl)-2-biphenylcarboxylic acid,
 30 (69) N-hydroxy-2'-(4-amidinophenylcarbamoyl)-4-((2-methylpropyl)carbamoyl)-2-biphenylcarboxamide,
 (70) N-hydroxy-2'-(4-amidinophenylcarbamoyl)-4'-methoxy-4-((2-methylpropyl)carbamoyl)-2-biphenylcarboxamide,
 (71) 2-[4-(4-amidinophenylcarbamoyl)-3-pyridyl]-5-[(1, 2, 2-trimethylpropyl)carbamoyl]benzoic acid,
 35 (72) 2-[2-(4-amidinophenylcarbamoyl)-6-methyl-3-pyridyl]-5-[(2-methylpropyl)carbamoyl]benzoic acid,
 (73) 2-[2-(4-amidinophenylcarbamoyl)-6-methyl-3-pyridyl]-5-[(1, 2, 2-trimethylpropyl)carbamoyl]benzoic acid,
 (74) 2'-(4-amidinophenylcarbamoyl)-4-(1, 1-dimethylpropylcarbamoyl)-2-biphenylcarboxylic acid,
 (75) 2'-(4-amidinophenylcarbamoyl)-4-[(1(S)-t-butyl-2-methoxycarbonyl)ethyl]carbamoyl]-2-biphenylcarboxylic acid,
 40 (76) 2'-(4-amidinophenylcarbamoyl)-4-(2, 2-dimethylcyclohexylcarbamoyl)-2-biphenylcarboxylic acid,
 (77) 2'-(4-amidinophenylcarbamoyl)-4-(1-isopropyl-2-methylpropylcarbamoyl)-2-biphenylcarboxylic acid,
 (78) 2'-(4-amidinophenylcarbamoyl)-4-[(4, 4-dimethyloxolan-3(S)-yl)carbamoyl]-2-biphenylcarboxylic acid,
 (79) 2-[2-(4-amidinophenylcarbamoyl)-3-pyridyl]-5-[(2-methylpropyl)carbamoyl]benzoic acid,
 (80) 2-[2-(4-amidinophenylcarbamoyl)-6-methyl-3-pyridyl]-5-[(3-hydroxymethyl-2, 2-dimethylpropyl)carbamoyl]benzoic acid,
 45 (81) 2-[2-(4-amidinophenylcarbamoyl)-3-pyridyl]-5-[(1, 2, 2-trimethylpropyl)carbamoyl]benzoic acid,
 (82) 2'-(4-amidinophenylcarbamoyl)-4-[(1(R), 2, 2-trimethylpropyl)carbamoyl]-2-biphenylcarboxylic acid,
 (83) 2'-(4-amidinophenylcarbamoyl)-4-[(1(S), 2, 2-trimethylpropyl)carbamoyl]-2-biphenylcarboxylic acid,
 (84) 2-[2-(4-amidinophenylcarbamoyl)-6-methyl-3-pyridyl]-5-[(2, 2-dimethylpropyl)carbamoyl]benzoic acid,
 50 (85) 2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-[(2-methylpropyl)carbamoyl]benzoic acid,
 (86) 2'-(4-amidinophenylcarbamoyl)-4-(1-methoxycarbonylcyclopentylcarbamoyl)-2-biphenylcarboxylic acid,
 (87) 2-[4-(4-amidinophenylcarbamoyl)-3-pyridyl]-5-[(1(S)-hydroxymethyl-2-methylpropyl)carbamoyl]benzoic acid,
 (88) 2-[2-(4-amidinophenylcarbamoyl)-6-methyl-3-pyridyl]-5-[(1(S)-hydroxymethyl-2-methylpropyl)carbamoyl]benzoic acid,
 55 (89) 2-[2-(4-amidinophenylcarbamoyl)-3-pyridyl]-5-[(1(S)-hydroxymethyl-2-methylpropyl)carbamoyl]benzoic acid,
 (90) 2'-(4-amidinophenylcarbamoyl)-4-[(2-methoxycarbonyl-2, 2-dimethylethyl)carbamoyl]-2-biphenylcarboxylic acid.

lic acid,

- (91) 2-[2-(4-amidinophenylcarbamoyl)-6-methyl-3-pyridyl]-5-[(1(S)-methoxycarbonyl-2-methylpropyl)carbamoyl]benzoic acid,
- (92) 2-[4-(4-amidinophenylcarbamoyl)-3-pyridyl]-5-[(1(S)-methoxycarbonyl-2-methylpropyl)carbamoyl]benzoic acid,
- (93) 2'-(4-amidino-3-hydroxyphenylcarbamoyl)-4-(2-methylpropylcarbamoyl)-2-biphenylcarboxylic acid,
- (94) 2'-(4-amidino-3-hydroxyphenylcarbamoyl)-4-(1, 2, 2-trimethylpropylcarbamoyl)-2-biphenylcarboxylic acid,
- (95) 2'-(4-amidinophenylcarbamoyl)-4-(1, 3-dimethylbutylcarbamoyl)-2-biphenylcarboxylic acid,
- (96) 2'-(4-amidinophenylcarbamoyl)-4-(2, 2-dimethyl-1(R)-cyclopentylcarbamoyl)-2-biphenylcarboxylic acid,
- (97) 2-[2-(4-amidinophenylcarbamoyl)-3-pyridyl]-5-[(1(S)-carboxy-2-methylpropyl)carbamoyl]benzoic acid,
- (98) 2-[3-(4-amidinophenylcarbamoyl)-2-furyl]-5-(2-methylpropylcarbamoyl)benzoic acid,
- (99) 2-[2-(4-amidinophenylcarbamoyl)-3-thienyl]-5-(2-methylpropylcarbamoyl)benzoic acid,
- (100) 2'-(4-amidinophenylcarbamoyl)-4-[(1-methoxycarbonyl-1-methylethyl)carbamoyl]-2-biphenylcarboxylic acid,
- (101) 2'-(4-amidinophenylcarbamoyl)-4-(1(S)-carboxy-3-methylbutylcarbamoyl)-2-biphenylcarboxylic acid,
- (102) 2-[2-(4-amidinophenylcarbamoyl)-3-pyridyl]-5-(2, 2-dimethylpropylcarbamoyl)benzoic acid,
- (103) 2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-(2, 2-dimethylpropylcarbamoyl)benzoic acid,
- (104) 2'-(4-amidinophenylcarbamoyl)-4-(2, 2-dimethyl-1(S)-cyclopentylcarbamoyl)-2-biphenylcarboxylic acid,
- (105) 2-[3-(4-amidinophenylcarbamoyl)-2-thienyl]-5-(2, 2-dimethylpropylcarbamoyl)benzoic acid,
- (106) 2-[2-(4-amidinophenylcarbamoyl)-3-thienyl]-5-(2, 2-dimethylpropylcarbamoyl)benzoic acid,
- (107) 2-[4-(4-amidinophenylcarbamoyl)-3-pyridyl]-5-(2, 2-dimethylpropylcarbamoyl)benzoic acid,
- (108) 2-[2-(4-amidinophenylcarbamoyl)-5-methyl-3-thienyl]-5-(2, 2-dimethylpropylcarbamoyl)benzoic acid,
- (109) 2'-(4-amidinophenylcarbamoyl)-4'-amino-4-(2, 2-dimethylpropylcarbamoyl)-2-biphenylcarboxylic acid,
- (110) 2-[2-(4-amidinophenylcarbamoyl)-5-methyl-3-furyl]-5-(2, 2-dimethylpropylcarbamoyl)benzoic acid,
- (111) 2-[4-(4-amidinophenylcarbamoyl)-2-methyl-pyrimidin-5-yl]-5-(2, 2-dimethylpropylcarbamoyl)benzoic acid,
- (112) 2-[2-(4-amidinophenylcarbamoyl)-6-methyl-3-pyridyl]-5-(1(S)-morpholinocarbonyl-3-methylbutylcarbamoyl)benzoic acid,
- (113) 2-[2-(4-amidinophenylcarbamoyl)-6-methyl-3-pyridyl]-5-(1(S)-methoxymethyl-2, 2-dimethylpropylcarbamoyl)benzoic acid,
- (114) 2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-(1(S)-methoxymethyl-2, 2-dimethylpropylcarbamoyl)benzoic acid,
- (115) 2-[2-(4-amidino-3-fluorophenylcarbamoyl)-6-methyl-3-pyridyl]-5-(2, 2-dimethylpropylcarbamoyl)benzoic acid,
- (116) 2'-(4-amidinophenylcarbamoyl)-5'-amino-4-(2, 2-dimethylpropylcarbamoyl)-2-biphenylcarboxylic acid,
- (117) 2-[2-(4-amidinophenylcarbamoyl)-6-methyl-3-pyridyl]-5-(1, 1, 3, 3-tetramethylbutylcarbamoyl)benzoic acid,
- (118) 2-[2-(4-amidinophenylcarbamoyl)-5-methyl-3-pyridyl]-5-(2, 2-dimethylpropylcarbamoyl)benzoic acid,
- (119) 2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-[[5-(1-methylethyl)-2, 2-dimethyldioxan-5-yl]carbamoyl]benzoic acid,
- (120) 2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-[1(S)-(4-ethoxycarbonyloxazol-2-yl)-3-methylbutylcarbamoyl]benzoic acid,
- (121) 2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-[(1(S)-N-hydroxycarbonyl)-3-methylbutylcarbamoyl]benzoic acid,
- (122) 2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-(2, 2-dimethylpropylcarbamoyl)-4-methylbenzoic acid,
- (123) 2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-(1(S)-hydroxymethyl-3-methylbutylcarbamoyl)-4-methylbenzoic acid,
- (124) 2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-[(4, 4-dimethyloxolan-3(S)-yl)carbamoyl]-4-methylbenzoic acid,
- (125) 2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-(1(R), 2, 2-trimethylpropylcarbamoyl)benzoic acid,
- (126) 2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-[(1(R)-2, 2-dimethylcyclopentyl)carbamoyl]benzoic acid,
- (127) 2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-[(1(S)-methylaminomethyl-3-methylbutyl)carbamoyl]benzoic acid,
- (128) 2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-[(4, 4-dimethyl-2-oxoxolan-3(S)-yl)carbamoyl]benzoic acid,

- (129) 2-[2-(4-amidinophenylcarbamoyl)-3-thienyl]-5-[(1(S)-acetyloxymethyl-2, 2-dimethylpropyl)carbamoyl]benzoic acid,
- (130) 2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-[[4-carboxy-4-(2-methyl-2-propenyl)piperidin-nyl]carbonyl]benzoic acid,
- (131) 2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-[(1(S)-[N-methyl-N-(1-iminoethyl)aminomethyl]-3-methylbutyl]benzoic acid,
- (132) 2'-(4-amidinophenylcarbamoyl)-4'-amino-4-(1(R), 2,2-trimethylpropylcarbamoyl)-2-biphenylcarboxylic acid,
- (133) 2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-[[1-(1-iminoethyl)-4-(2-methylpropyl)piperidin-4-yl]carbamoyl]benzoic acid,
- (134) 3-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-6-[(1(R), 2, 2-trimethylpropyl)carbamoyl]-2-pyridinecarboxylic acid,
- (135) 2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-(t-butylcarbamoyl)benzoic acid,
- (136) 2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-(2, 2, 2-trichloroethylcarbamoyl)benzoic acid,
- (137) 2-[3-(4-amidinophenylcarbamoyl)-2-thienyl]-6-(t-butylcarbamoyl)-2-pyridinecarboxylic acid,
- (138) 2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-(2, 2, 2-trifluoroethylcarbamoyl)benzoic acid,
- (139) 2-[2-[(2-amidinopyrimidin-5-yl)carbamoyl]-6-methoxy-3-pyridyl]-5-(2, 2-dimethylpropylcarbamoyl)benzoic acid,
- (140) 2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-[[1(S)-(2-aminoethyl)-3-methylbutyl]carbamoyl]benzoic acid,
- (141) 2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-[(2, 2-dimethyl-3-hydroxypropyl)carbamoyl]benzoic acid,
- (142) 2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-[(2, 2-diethylbutyl)carbamoyl]benzoic acid,
- (143) 2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-[(1-hydroxymethyl)cyclobutylmethyl]carbamoyl]benzoic acid,
- (144) 2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-[(2-ethyl-2-hydroxymethylbutyl)carbamoyl]benzoic acid,
- (145) 2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-[(1-hydroxymethyl)cyclopentylmethyl]carbamoyl]benzoic acid,
- (146) 2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-[(2-propyl-2-hydroxymethylpentyl)carbamoyl]benzoic acid,
- (147) 2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-[(2-(2-methylpropyl)-2-hydroxymethyl-4-methylpentyl)carbamoyl]benzoic acid,
- (148) 2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-[(1-hydroxymethylcyclopentyl)carbamoyl]benzoic acid,
- (149) 2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-[(1-(2-methylpropyl)-1-hydroxymethyl-3-methylbutyl)carbamoyl]benzoic acid,
- (150) 2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-[(1(S)-(hydroxymethyl)-2(S)-methylbutyl)carbamoyl]benzoic acid,
- (151) 2-[2-(4-amidinophenylcarbamoyl)-6-ethoxy-3-pyridyl]-5-[(1(S)-isopropyl-3-aminopropyl)carbamoyl]benzoic acid,
- (152) 2-[2-(4-amidinophenylcarbamoyl)-6-ethoxy-3-pyridyl]-5-[(1(S)-(2-aminoethyl)-3-methylbutyl)carbamoyl]benzoic acid,
- (153) 2-[2-(4-amidinophenylcarbamoyl)-6-ethoxy-3-pyridyl]-5-[(1(S)-(2-aminoethyl)-2(S)-methylbutyl)carbamoyl]benzoic acid,
- (154) 2'-(4-amidinophenylcarbamoyl)-4-[(1(S)-carboxymethyl-2, 2-dimethylpropyl)carbamoyl]-2-biphenylcarboxylic acid,
- (155) 2'-(4-amidinophenylcarbamoyl)-4-(1-carboxycyclopentylcarbamoyl)-2-biphenylcarboxylic acid,
- (156) 2'-(4-amidinophenylcarbamoyl)-4-[[2-carboxy-2, 2-dimethylethyl]carbamoyl]-2-biphenylcarboxylic acid,
- (157) 2-[2-(4-amidinophenylcarbamoyl)-6-methyl-3-pyridyl]-5-[(1(S)-carboxy-2-methylpropyl)carbamoyl]benzoic acid,
- (158) 2-[4-(4-amidinophenylcarbamoyl)-3-pyridyl]-5-[(1(S)-carboxy-2-methylpropyl)carbamoyl]benzoic acid,
- (159) 2'-(4-amidinophenylcarbamoyl)-4-[(1-carboxy-1-methylethyl)carbamoyl]-2-biphenylcarboxylic acid,
- (160) 2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-[1(S)-(4-carboxyoxazol-2-yl)-3-methylbutyl]carbamoyl]benzoic acid,
- (161) 2'-(4-amidinophenylcarbamoyl)-4-(2, 2-dimethylcyclopentylcarbamoyl)-2-biphenylcarboxylic acid,
- (162) 2'-(4-amidinophenylcarbamoyl)-4-[(N-methyl-N-t-butylamino)carbamoyl]-2-biphenylcarboxylic acid,
- (163) 2-[2-(4-amidinophenylcarbamoyl)-6-methyl-3-pyridyl]-5-[(3-methyl-2-butenyl)carbamoyl]benzoic acid,

- (164) 2'-(4-amidinophenylcarbamoyl)-5'-nitro-4-(2, 2-dimethylpropylcarbamoyl)-2-biphenylcarboxylic acid;
- (165) 3-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-6-[(1-isopropyl-2-methylpropyl)carbamoyl]-2-pyridinecarboxylic acid,
- 5 (166) 2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-[(1(S)-hydroxymethyl-2, 2-dimethylpropyl)carbamoyl]benzoic acid,
- (167) 2'-[(2-amidino-5-pyridyl)carbamoyl]-4'-methoxy-4-[(1(S)-hydroxymethyl-2, 2-dimethylpropyl)carbamoyl]-2-biphenylcarboxylic acid,
- (168) 2'-[(2-amidino-5-pyridyl)carbamoyl]-4-[(1(S)-hydroxymethyl-2, 2-dimethylpropyl)carbamoyl]-2-biphenylcarboxylic acid,
- 10 (169) 2-[4-(4-amidinophenylcarbamoyl)-3-pyridyl]-5-[(1(S)-hydroxymethyl-2, 2-dimethylpropyl)carbamoyl]benzoic acid,
- (170) 2-[4-[(2-amidino-5-pyridyl)carbamoyl]-3-pyridyl]-5-[(1(S)-hydroxymethyl-2, 2-dimethylpropyl)carbamoyl]benzoic acid,
- (171) 2-[2-(4-amidinophenylcarbamoyl)-3-pyridyl]-5-[(1(S)-hydroxymethyl-2, 2-dimethylpropyl)carbamoyl]benzoic acid,
- 15 (172) 2-[2-[(2-amidino-5-pyridyl)carbamoyl]-3-pyridyl]-5-[(1(S)-hydroxymethyl-2, 2-dimethylpropyl)carbamoyl]benzoic acid,
- (173) 2-[2-(4-amidinophenylcarbamoyl)-6-methyl-3-pyridyl]-5-[(1(S)-hydroxymethyl-2, 2-dimethylpropyl)carbamoyl]benzoic acid,
- 20 (174) 2-[2-(4-amidinophenylcarbamoyl)-6-methyl-3-pyridyl]-5-[(1(S)-hydroxymethyl-3-methylbutyl)carbamoyl]benzoic acid,
- (175) 2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-4-methyl-5-[(1(S)-hydroxymethyl-2, 2-dimethylpropyl)carbamoyl]benzoic acid,
- (176) 2-[3-(4-amidinophenylcarbamoyl)-2-thienyl]-5-[(1(S)-hydroxymethyl-2, 2-dimethylpropyl)carbamoyl]benzoic acid,
- 25 (177) 2-[2-(4-amidinophenylcarbamoyl)-3-thienyl]-5-[(1(S)-hydroxymethyl-2, 2-dimethylpropyl)carbamoyl]benzoic acid,
- (178) 2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-[(1-hydroxymethyl-1-methoxycarbonyl-3-methylbutyl)carbamoyl]benzoic acid,
- 30 (179) 2-[2-[N-(4-amidinophenyl)-N-methylcarbamoyl]-6-methoxy-3-pyridyl]-5-[(1(S)-hydroxymethyl-2, 2-dimethylpropyl)carbamoyl]benzoic acid,
- (180) 2-[2-(4-amidinophenylcarbamoyl)-6-ethoxy-3-pyridyl]-5-[(1(S)-hydroxymethyl-2, 2-dimethylpropyl)carbamoyl]benzoic acid,
- (181) 2-[2-(4-amidinophenylcarbamoyl)-6-isopropoxy-3-pyridyl]-5-[(1(S)-hydroxymethyl-2, 2-dimethylpropyl)carbamoyl]benzoic acid,
- 35 (182) 2-[2-(4-amidinophenylcarbamoyl)-6-chloro-3-pyridyl]-5-[(1(S)-hydroxymethyl-2, 2-dimethylpropyl)carbamoyl]benzoic acid,
- (183) 2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-[(1(S)-(2-hydroxyethyl)-2, 2-dimethylpropyl)carbamoyl]benzoic acid,
- 40 (184) 3-[3-(4-amidinophenylcarbamoyl)-2-thienyl]-6-[(1(S)-hydroxymethyl-2, 2-dimethylpropyl)carbamoyl]-2-pyridinecarboxylic acid,
- (185) 3-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-6-[(1(S)-hydroxymethyl-2, 2-dimethylpropyl)carbamoyl]-2-pyridinecarboxylic acid,
- (186) 2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-[(1(S)-(2-hydroxyethylcarbamoyl)-3-methylbutyl)carbamoyl]benzoic acid,
- 45 (187) 3-[2-(2-amidino-5-pyridylcarbamoyl)-6-methoxy-3-pyridyl]-6-[(1(S)-hydroxymethyl-2, 2-dimethylpropyl)carbamoyl]-2-pyridinecarboxylic acid,
- (188) 2-[2-(4-amidinophenylcarbamoyl)-6-dimethylamino-3-pyridyl]-5-[(1(S)-hydroxymethyl-2, 2-dimethylpropyl)carbamoyl]benzoic acid,
- 50 (189) 2-[2-(4-amidinophenylcarbamoyl)-6-butoxy-3-pyridyl]-5-[(1(S)-hydroxymethyl-2, 2-dimethylpropyl)carbamoyl]benzoic acid,
- (190) 2-[2-(2-amidinopyrimidin-5-yl)carbamoyl]-6-methoxy-3-pyridyl]-5-[(1(S)-hydroxymethyl-2, 2-dimethylpropyl)carbamoyl]benzoic acid,
- (191) 2-[2-(4-amidinophenylcarbamoyl)-6-propoxy-3-pyridyl]-5-[(1(S)-hydroxymethyl-2, 2-dimethylpropyl)carbamoyl]benzoic acid,
- 55 (192) 2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-[(1(S), 2-bishydroxymethyl-2-methylpropyl)carbamoyl]benzoic acid,
- (193) 2-[2-(4-amidinophenylcarbamoyl)-6-ethoxy-3-pyridyl]-5-[(1(S), 2-bishydroxymethyl-2-methylpropyl)car-

bamoyl]benzoic acid,

(194) 5-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-2-[(1(S)-hydroxymethyl-2, 2-dimethylpropyl)carbamoyl]-4-pyridinecarboxylic acid,

(195) 2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-[(1(S)-hydroxymethyl-2-methylpropyl)carbamoyl]benzoic acid,

(196) 2-[2-(4-amidinophenylcarbamoyl)-6-ethoxy-3-pyridyl]-5-[(1(S)-hydroxymethyl-3, 3-dimethylbutyl)carbamoyl]benzoic acid,

(197) 2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-[(1(S)-hydroxymethyl-3, 3-dimethylbutyl)carbamoyl]benzoic acid,

(198) 2'-(4-amidinophenylcarbamoyl)-4'-hydroxymethyl-4-(2-methylpropylcarbamoyl)-2-biphenylcarboxylic acid,

(199) 2'-(4-amidinophenylcarbamoyl)-4'-hydroxymethyl-4-(1, 2, 2-trimethylpropylcarbamoyl)-2-biphenylcarboxylic acid,

(200) 3-[2-(4-amidinophenylcarbamoyl)-4-methoxyphenyl]-6-[(1(S)-hydroxymethyl-2, 2-dimethylpropyl)carbamoyl]-2-pyridinecarboxylic acid,

(201) 2-[2-(4-amidinophenylcarbamoyl)phenyl]-5-(2, 2-dimethylpropylcarbamoyl)-3-furancarboxylic acid,

(202) 2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-[(3-amino-1(S)-t-butylpropyl)carbamoyl]benzoic acid,

(203) 2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-[(1, 1-bishydroxymethyl-2-methylpropyl)carbamoyl]benzoic acid,

(204) 2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-[(4-(2-methylpropyl)-4-piperidino)carbamoyl]benzoic acid,

(205) 2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-[(2-amino-3-methylbutyl)carbamoyl]benzoic acid,

(206) 2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-[(1(S)-(4-aminobutylcarbamoyl)-3-methylbutyl)carbamoyl]benzoic acid,

(207) 2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-[(3-amino-2, 2-dimethylpropyl)carbamoyl]benzoic acid,

(208) 2-[2-(4-amidinophenylcarbamoyl)-6-ethoxy-3-pyridyl]-5-[(3-amino-1(S)-t-butylpropyl)carbamoyl]benzoic acid,

(209) 2-[2-(4-amidinophenylcarbamoyl)-6-ethoxy-3-pyridyl]-5-[(4-amino-1(S)-t-butylbutyl)carbamoyl]benzoic acid,

(210) N-hydroxy-2'-(4-amidinophenylcarbamoyl)-4'-[(1(R), 2, 2-trimethylpropyl)carbamoyl]-2-biphenylcarboxamide,

(211) 2'-(4-amidinobenzoyloxy)-4-(2-methylpropylcarbamoyl)-2-biphenylcarboxylic acid,

(212) 2'-(4-amidinobenzoyloxy)-4-(1(S)-hydroxymethyl-2, 2-dimethylpropylcarbamoyl)-2-biphenylcarboxylic acid,

(213) 2'-(4-amidinobenzoyloxy)-4'-methyl-4-(1(S)-hydroxymethyl-2, 2-dimethylpropylcarbamoyl)-2-biphenylcarboxylic acid,

(214) 2'-(4-amidinophenylaminomethyl)-4-(1(S)-hydroxymethyl-2, 2-dimethylpropylcarbamoyl)-2-biphenylcarboxylic acid,

(215) 2-[2-(4-amidinophenylaminomethyl)-3-pyridyl]-5-(2-methylpropylcarbamoyl)benzoic acid,

(216) 2-[2-(4-amidinophenylaminomethyl)-6-methyl-3-pyridyl]-5-(2-methylpropylcarbamoyl)benzoic acid,

(217) 2-[4-(4-amidinophenylaminomethyl)-3-pyridyl]-5-(2-methylpropylcarbamoyl)benzoic acid,

methyl ester, ethyl ester, benzyl ester thereof, non-toxic salts thereof or hydroxide thereof.

8. The compound according to claim 1, which is selected from

(1) 2'-(4-amidinophenylcarbamoyl)-4'-methyl-2-biphenylcarboxylic acid,

(2) 2'-(4-amidinophenylcarbamoyl)-4'-[(1-carboxy-2-methylpropyl)carbamoyl]-2-biphenylcarboxylic acid,

(3) 2'-(4-amidinophenylcarbamoyl)-2-biphenylcarboxylic acid,

(4) 2, 3-dihydro-2, 2-dimethyl-5-(2-(4-amidinophenylcarbamoyl)phenyl)-6-benzofurancarboxylic acid,

(5) 2'-(4-amidinophenylcarbamoyl)-2, 3-biphenyldicarboxylic acid,

(6) 2'-(4-amidinophenylcarbamoyl)-6-methyl-2-biphenylcarboxylic acid,

(7) 2'-(4-amidinophenylcarbamoyl)-5-methoxy-2-biphenylcarboxylic acid,

(8) 2'-(4-amidinophenylcarbamoyl)-4-methoxy-2-biphenylcarboxylic acid,

(9) 2'-(4-amidinophenylcarbamoyl)-6-methoxy-2-biphenylcarboxylic acid,

(10) 2'-(4-amidinophenylcarbamoyl)-4-hydroxy-2-biphenylcarboxylic acid,

- (11) 2'-(4-amidinophenylcarbamoyl)-5-hydroxy-2-biphenylcarboxylic acid,
- (12) 2'-(4-amidinophenylcarbamoyl)-5-methyl-2-biphenylcarboxylic acid,
- (13) 2'-(4-amidinophenylcarbamoyl)-4-methyl-2-biphenylcarboxylic acid,
- (14) 2'-(4-amidinophenylcarbamoyl)-3-hydroxy-2-biphenylcarboxylic acid,
- 5 (15) 2'-(4-amidinophenylcarbamoyl)-4'-methyl-5-chloro-2-biphenylcarboxylic acid,
- (16) 2'-(4-amidinophenylcarbamoyl)-3-methoxy-2-biphenylcarboxylic acid,
- (17) 2'-(4-amidinophenylcarbamoyl)-4'-methyl-4-methoxy-2-biphenylcarboxylic acid,
- (18) 2-(2-(4-amidinophenylcarbamoyl)phenyl)-1-naphthalenecarboxylic acid,
- (19) 2'-(4-amidinophenylcarbamoyl)-3-methyl-2-biphenylcarboxylic acid,
- 10 (20) 3-(2-(4-amidinophenylcarbamoyl)phenyl)-7-methoxy-2-naphthalenecarboxylic acid,
- (21) 3-(2-(4-amidinophenylcarbamoyl)phenyl)-5-methoxy-2-naphthalenecarboxylic acid,
- (22) 2'-(4-amidinophenylcarbamoyl)-2, 4-biphenyldicarboxylic acid,
- (23) 3-(2-(4-amidinophenylcarbamoyl)phenyl)-6-methoxy-2-naphthalenecarboxylic acid,
- (24) 3-(2-(4-amidinophenylcarbamoyl)phenyl)-8-methoxy-2-naphthalenecarboxylic acid,
- 15 (25) 2'-(4-amidinophenylcarbamoyl)-3, 4-dimethoxy-2-biphenylcarboxylic acid,
- (26) 6-(2-(4-amidinophenylcarbamoyl)phenyl)-1, 2-methylenedioxybenzen-5-carboxylic acid,
- (27) 2'-(4-amidinophenylcarbamoyl)-4'-nitro-2-biphenylcarboxylic acid,
- (28) 2'-(4-amidinophenylcarbamoyl)-2-biphenylphosphoric acid,
- (29) 2'-(4-amidinophenylcarbamoyl)-4-fluoro-2-biphenylcarboxylic acid,
- 20 (30) 2'-(4-amidinophenylcarbamoyl)-4-(2-methoxycarbonylethyl)-2-biphenylcarboxylic acid,
- (31) 2'-(4-amidinophenylcarbamoyl)-4-(2-methoxyethoxy)-2-biphenylcarboxylic acid,
- (32) 2'-(4-amidinophenylcarbamoyl)-4-trifluoromethoxy-2-biphenylcarboxylic acid,
- (33) 3-(2-(4-amidinophenylcarbamoyl)phenyl)-8-(2-methoxyethoxy)-2-naphthalenecarboxylic acid,
- (34) 2'-(4-amidinophenylcarbamoyl)-4-((isopropylcarbonyl)aminomethyl)-2-biphenylcarboxylic acid,
- 25 (35) 2'-(4-amidinophenylcarbamoyl)-4-((2-methylpropyl)sulfamoyl)-2-biphenylcarboxylic acid,
- (36) 2'-(4-amidinophenylcarbamoyl)-5-chloro-2-biphenylcarboxylic acid,
- (37) 3-(2-(4-amidinophenylcarbamoyl)phenyl)-2-naphthalenecarboxylic acid,
- (38) 2'-(3-amidinophenylcarbamoyl)-2-biphenylcarboxylic acid,
- (39) 2-(2-(4-amidinophenylcarbamoyl)phenyl)cinnamic acid,
- 30 (40) 2'-(4-amidinophenylcarbamoyl)biphenyl-2-yloxyacetic acid,
- (41) 3-(2-(4-amidinophenylcarbamoyl)-4-methylphenyl)-2-naphthalenecarboxylic acid,
- (42) 1-(2-(4-amidinophenylcarbamoyl)phenyl)-2-naphthalenecarboxylic acid,
- (43) 3-(2-(4-amidinophenylcarbamoyl)-4-methoxyphenyl)-2-naphthalenecarboxylic acid,
- (44) 3-(2-(4-amidinophenylcarbamoyl)-4-propoxyphenyl)-2-naphthalenecarboxylic acid,
- 35 (45) 2'-(4-amidinophenylcarbamoyl)-4-nitro-2-biphenylcarboxylic acid,
- (46) 2'-(4-amidinophenylcarbamoyl)-4-methylsulfonylamino-2-biphenylcarboxylic acid,
- (47) 2'-(4-amidinophenylcarbamoyl)-4-chloro-2-biphenylcarboxylic acid,
- (48) 2'-(4-amidinophenylcarbamoyl)biphenyl-2-ylacetic acid,
- (49) 2'-(4-amidinophenylcarbamoyl)-5-nitro-2-biphenylcarboxylic acid,
- 40 (50) 2'-(4-amidinophenylcarbamoyl)-4-methylaminomethyl-2-biphenylcarboxylic acid,
- (51) 2'-(4-amidinophenylcarbamoyl)-4-ethoxycarbonylmethoxy-2-biphenylcarboxylic acid,
- (52) 2'-(4-amidinophenylcarbamoyl)-4-(2-(methoxymethoxy)ethoxy)biphenylcarboxylic acid,
- (53) 3-(2-(4-amidinophenylcarbamoyl)phenyl)-5-methoxymethoxy-2-naphthalenecarboxylic acid,
- (54) 3-(2-(4-amidinophenylcarbamoyl)phenyl)-8-methoxymethoxy-2-naphthalenecarboxylic acid,
- 45 (55) 2'-(4-amidinophenylcarbamoyl)-4'-amino-2-biphenylcarboxylic acid,
- (56) 2'-(4-amidinophenylcarbamoyl)-4'-chloro-2-biphenylcarboxylic acid,
- (57) 2'-(4-amidinophenylcarbamoyl)-4'-(2-methoxycarbonylethyl)-2-biphenylcarboxylic acid,
- (58) 2'-(4-amidinophenylcarbamoyl)-3'-benzyloxy-2-biphenylcarboxylic acid,
- (59) 2'-(4-amidinophenylcarbamoyl)-6'-methyl-2-biphenylcarboxylic acid,
- 50 (60) 2'-(4-amidinophenylcarbamoyl)-5'-methyl-2-biphenylcarboxylic acid,
- (61) 2'-(4-amidinophenylcarbamoyl)-4'-isopropyl-2-biphenylcarboxylic acid,
- (62) 2'-(4-amidinophenylcarbamoyl)-4'-t-butyl-2-biphenylcarboxylic acid,
- (63) 2'-(4-amidinophenylcarbamoyl)-4'-ethyl-2-biphenylcarboxylic acid,
- (64) 2'-(4-amidinophenylcarbamoyl)-4'-methoxy-2-biphenylcarboxylic acid,
- 55 (65) 2'-(4-amidinophenylcarbamoyl)-4'-ciano-2-biphenylcarboxylic acid,
- (66) 2'-(4-amidinophenylcarbamoyl)-5'-methoxy-2-biphenylcarboxylic acid,
- (67) 2'-(4-amidinophenylcarbamoyl)-6'-methoxy-2-biphenylcarboxylic acid,
- (68) 2'-(4-amidinophenylcarbamoyl)-5'-chloro-4-methyl-2-biphenylcarboxylic acid,

- (69) 2'-(4-amidinophenylcarbamoyl)-4'-methoxy-4-methyl-2-biphenylcarboxylic acid,
 (70) 2'-(4-amidinophenylcarbamoyl)-4'-dimethylcarbamoyl-2-biphenylcarboxylic acid,
 (71) 2'-(4-amidinophenylcarbamoyl)-2, 4'-biphenyldicarboxylic acid,
 (72) 2'-(4-amidinophenylcarbamoyl)-4'-methylcarbamoyl-2-biphenylcarboxylic acid,
 (73) 2'-(4-amidinophenylcarbamoyl)-4'-methylaminomethyl-2-biphenylcarboxylic acid,
 (74) 2'-(4-amidinophenylcarbamoyl)-4'-(2-hydroxyethoxy)-2-biphenylcarboxylic acid,
 (75) 2'-(4-amidinophenylcarbamoyl)-4'-fluoro-2-biphenylcarboxylic acid,
 (76) 2'-(4-amidinophenylcarbamoyl)-4'-(2-methoxyethoxy)-2-biphenylcarboxylic acid,
 (77) 2'-(4-amidinophenylcarbamoyl)-4'-trifluoromethoxy-2-biphenylcarboxylic acid,
 (78) 2'-(4-amidinophenylcarbamoyl)-4'-((methoxycarbonylmethyl)carbamoyl)-2-biphenylcarboxylic acid,
 (79) 2'-(4-amidinophenylcarbamoyl)-4'-((1-methoxycarbonyl-2-phenylethyl)carbamoyl)-2-biphenylcarboxylic acid,
 (80) 2'-(4-amidinophenylcarbamoyl)-4'-ethoxycarbonylmethoxybiphenylcarboxylic acid,
 (81) 2'-(4-amidinophenylcarbamoyl)-4'-hydroxy-2-biphenylcarboxylic acid,
 (82) 2'-(4-amidinophenylcarbamoyl)-5'-hydroxy-2-biphenylcarboxylic acid,
 (83) 2'-(4-amidinophenylcarbamoyl)-4'-bromo-2-biphenylcarboxylic acid,
 (84) 2'-(4-amidinophenylcarbamoyl)-4-bromo-2-biphenylcarboxylic acid,
 (85) 2'-(4-amidinophenylcarbamoyl)-3'-methoxy-2-biphenylcarboxylic acid,
 (86) 2'-(4-amidinophenylaminomethyl)-2-biphenylcarboxylic acid,
 (87) 2'-(4-amidinophenylaminomethyl)-4'-methoxy-2-biphenylcarboxylic acid,
 (88) 2'-(4-(N²-t-butoxycarbonyloxyamidino)phenylcarbamoyl)-2-biphenylcarboxylic acid,
 (89) 2'-(4-(N²-ethoxycarbonylamidino)phenylcarbamoyl)-2-biphenylcarboxylic acid,
 (90) 2-(4-amidinophenylcarbamoyl)pyridin-3-yl)benzoic acid,
 (91) 2'-(4-amidinophenylcarbamoyl)-4-(3-methylbutoxy)-2-biphenylcarboxylic acid,
 (92) 2'-(4-amidinophenylcarbamoyl)-4-methylaminomethyl-2-biphenylcarboxylic acid,
 (93) 2'-(4-amidinophenylcarbamoyl)-4-carboxymethoxy-2-biphenylcarboxylic acid,
 (94) 2'-(4-amidinophenylcarbamoyl)-4-(2-hydroxyethoxy)-2-biphenylcarboxylic acid,
 (95) 3-(2-(4-amidinophenylcarbamoyl)phenyl)-5-hydroxy-2-naphthalenecarboxylic acid,
 (96) 3-(2-(4-amidinophenylcarbamoyl)phenyl)-8-hydroxy-2-naphthalenecarboxylic acid,
 (97) 2'-(4-amidinophenylcarbamoyl)-4-((2-methylpropyl)aminomethyl)-2-biphenylcarboxylic acid,
 (98) 2'-(4-amidinophenylcarbamoyl)-3'-hydroxy-2-biphenylcarboxylic acid,
 (99) 2'-(4-amidinophenylcarbamoyl)-4'-((carboxymethyl)carbamoyl)-2-biphenylcarboxylic acid,
 (100) 2'-(4-amidinophenylcarbamoyl)-4'-((1-carboxy-2-phenylethyl)carbamoyl)-2-biphenylcarboxylic acid,
 (101) 2'-(4-amidinophenylcarbamoyl)-4'-carboxymethoxy-2-biphenylcarboxylic acid,
 (102) 2'-(4-(N²-hydroxyamidino)phenylcarbamoyl)-2-biphenylcarboxylic acid,
 (103) N-hydroxy-2'-(4-amidinophenylcarbamoyl)-2-biphenylcarboxamide,
 (104) N-hydroxy-N-methyl-2'-(4-amidinophenylcarbamoyl)-2-biphenylcarboxamide,
 (105) N-hydroxy-2'-(4-amidinophenylcarbamoyl)-4'-methyl-2-biphenylcarboxamide,
 (106) N-hydroxy-2'-(4-amidinophenylcarbamoyl)-4'-methoxy-2-biphenylcarboxamide,
 (107) N-hydroxy-2'-(4-(N²-ethoxycarbonylamidino)phenylcarbamoyl)-2-biphenylcarboxamide,
 (108) 2'-(4-amidinophenylcarbamoyl)-4-amino-2-biphenylcarboxylic acid,
 (109) 3-(2'-(4-amidinophenylcarbamoyl)biphenyl-2-yl)propanoic acid,
 (110) 2'-(4-amidinophenylcarbamoyl)-4-methylcarbonylamino-2-biphenylcarboxylic acid,
 (111) 2'-(4-amidinophenylcarbamoyl)-4'-methylcarbonylamino-2-biphenylcarboxylic acid,
 (112) 2'-(4-amidinophenylcarbamoyl)-4-((2-methylpropylcarbonyl)amino)-2-biphenylcarboxylic acid,
 (113) N-hydroxy-2'-(4-(N²-hydroxyamidino)phenylcarbamoyl)-2-biphenylcarboxamide,
 (114) 2'-(4-(N²-(2-propenyl)oxycarbonylamidino)phenylcarbamoyl)-2-biphenylcarboxylic acid,
 (115) 2'-(1-(4-amidinophenylamino)-1-methoxycarbonylmethyl)-2-biphenylcarboxylic acid,
 (116) 2'-(1-(4-amidinophenylamino)-1-methylcarbamoylmethyl)-2-biphenylcarboxylic acid,
 (117) 2'-(1-(4-amidinophenylamino)-1-cyanomethyl)-2-biphenylcarboxylic acid,
 (118) 2'-(1-(4-amidinophenylamino)-1-carboxymethyl)-2-biphenylcarboxylic acid,
 (119) 2'-(4-amidinobenzoyloxy)-2-biphenylcarboxylic acid,
 (120) 2'-(4-amidinophenylcarbamoyl)-2-(tetrazol-5-yl)biphenyl,
 (121) 2-[2-(4-amidinophenylcarbamoyl)-6-methyl-3-pyridyl]-5-(2, 2-dimethylpropyloxycarbonyl)benzoic acid,
 (122) 4-[2-(4-amidinophenylcarbamoyl)-6-methyl-3-pyridyl]isophthalic acid,
 (123) 4-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]isophthalic acid,
 (124) 2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-[1-(2, 2-dimethylpropyl)tetrazol-5-yl]benzoic acid,

(125) 2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-[(2, 2-diethylbutyloxy)carbamoyl]benzoic acid,
 (126) 2'-(4-amidinophenylcarbamoyl)-4-(3-methylbutylcarbonyl)-2-biphenylcarboxylic acid,
 (127) 2-[2-(4-amidinophenylcarbamoyl)-6-methoxy-3-pyridyl]-5-[(2-amino-2-hydroxymethyl-3-methylbutyl)carbamoyl]benzoic acid,
 methyl ester, ethyl ester, benzyl ester thereof, non-toxic salts thereof or hydroxide thereof.

9. The compound according to claim 1, which is selected from

(1) 3-(4-amidinophenylcarbamoyl)-4-biphenylcarboxylic acid,
 (2) 4-(4-amidinophenylcarbamoyl)-3-biphenylcarboxylic acid,
 (3) 3'-(4-amidinophenylcarbamoyl)-2-biphenylcarboxylic acid,
 (4) 2'-(4-amidinophenylcarbamoyl)-3-biphenylcarboxylic acid,
 (5) 2'-(4-amidinophenylcarbamoyl)-4-biphenylcarboxylic acid,
 (6) 2'-(4-amidinophenoxymethyl)-4-[(2-methylpropyl)carbamoyl]-2-biphenylcarboxylic acid,
 (7) 2'-(4-amidinophenylthiomethyl)-4-[(2-methylpropyl)carbamoyl]-2-biphenylcarboxylic acid,
 (8) 2'-(4-amidinophenylethynyl)-4-[(2-methylpropyl)carbamoyl]-2-biphenylcarboxylic acid,
 (9) 2'-(4-amidinophenylethynyl)-2-biphenylcarboxylic acid,
 (10) 2'-[(1E)-2-(4-amidinophenyl)ethenyl]-4-[(2-methylpropyl)carbamoyl]-2-biphenylcarboxylic acid,
 (11) 2'-[(1E)-2-(4-amidinophenyl)ethenyl]-2-biphenylcarboxylic acid,
 (12) 2'-(2-(4-amidinophenyl)ethyl)-4-[(2-methylpropyl)carbamoyl]-2-biphenylcarboxylic acid,
 (13) 2'-(2-(4-amidinophenyl)ethyl)-2-biphenylcarboxylic acid,
 (14) 2-[2-(4-amidinophenoxycarbonyl)-6-methoxy-3-pyridyl]-5-[(1S)-hydroxymethyl-2, 2-dimethylpropyl]carbamoyl]benzoic acid,
 methyl ester, ethyl ester, benzyl ester thereof, non-toxic salts thereof or hydroxide thereof.

10. The compound according to claim 1, which is selected from

(1) 2-(3-(4-amidinophenylcarbamoyl)naphthalen-2-yl)benzoic acid,
 (2) 2-(3-(4-amidinophenylcarbamoyl)naphthalen-2-yl)-5-[(1-methoxycarbonyl-2-methylpropyl)carbamoyl]benzoic acid,
 (3) 2-(3-(4-amidinophenylcarbamoyl)naphthalen-2-yl)-5-[(2-methylpropyl)carbamoyl]benzoic acid,
 (4) 2-(3-(4-amidinophenylcarbamoyl)-6-methoxynaphthalen-2-yl)benzoic acid,
 (5) 2-(3-(4-amidinophenylcarbamoyl)-7-methoxynaphthalen-2-yl)benzoic acid,
 (6) 2-(3-(4-amidinophenylcarbamoyl)-5-methoxynaphthalen-2-yl)benzoic acid,
 (7) 2-(3-(4-amidinophenylcarbamoyl)naphthalen-2-yl)-5-methylbenzoic acid,
 (8) 2-(2-(4-amidinophenylcarbamoyl)naphthalen-1-yl)benzoic acid,
 (9) 2-(3-(4-amidinophenylcarbamoyl)naphthalen-2-yl)-5-methoxybenzoic acid,
 (10) 2-(3-(4-amidinophenylcarbamoyl)naphthalen-2-yl)-5-propoxybenzoic acid,
 (11) 2-(2, 3-dihydro-2, 2-dimethyl-6-(4-amidinophenylcarbamoyl)benzofuran-5-yl)benzoic acid,
 (12) 2-(5, 6, 7, 8-tetrahydro-3-(4-amidinophenylcarbamoyl)naphthalen-2-yl)benzoic acid,
 (13) 2-(6-(4-amidinophenylcarbamoyl)indan-5-yl)benzoic acid,
 (14) 2-(3-(4-amidinophenylcarbamoyl)-8-methoxynaphthalen-2-yl)benzoic acid,
 (15) 2-(6-(4-amidinophenylcarbamoyl)-1, 2-methylenedioxybenzen-5-yl)benzoic acid,
 (16) 2-(3-(4-amidinophenylcarbamoyl)-8-hydroxynaphthalen-2-yl)benzoic acid,
 (17) 2-(3-(4-amidinophenylcarbamoyl)-5-(2-methoxyethoxy)naphthalen-2-yl)benzoic acid,
 (18) 2-(3-(4-amidinophenylcarbamoyl)-5-hydroxynaphthalen-2-yl)benzoic acid,
 (19) 2-(6-(4-amidinophenylcarbamoyl)-1-benzylloxymethylbenzimidazol-5-yl)benzoic acid,
 (20) 2-(5-(4-amidinophenylcarbamoyl)-1-benzylloxymethylbenzimidazol-6-yl)benzoic acid,
 (21) 2-(6-(4-amidinophenylcarbamoyl)benzofuran-5-yl)benzoic acid,
 (22) 2-(5-(4-amidinophenylcarbamoyl)benzofuran-6-yl)benzoic acid,
 (23) 2-(3-(4-amidinophenylaminomethyl)naphthalen-2-yl)benzoic acid,
 (24) 2-(3-(4-amidinophenylaminomethyl)naphthalen-2-yl)-5-[(2-methylpropyl)carbamoyl]benzoic acid,
 (25) 2-(2-(4-amidinophenylcarbamoyl)benzothiophene-3-yl)benzoic acid,
 (26) 2-(3-(4-amidinophenylcarbamoyl)-5-methoxybenzofuran-2-yl)benzoic acid,
 (27) 2-(6-(4-amidinophenylcarbamoyl)benzimidazol-5-yl)benzoic acid,
 (28) N-hydroxy-2-(3-(4-amidinophenylcarbamoyl)naphthalen-2-yl)-5-[(2-methylpropyl)carbamoyl]benzcarboxamide,
 (29) N-hydroxy-2-(3-(4-amidinophenylcarbamoyl)naphthalen-2-yl)benzcarboxamide,

(30) N-hydroxy-2-(3-(4-amidinophenylcarbamoyl)naphthalen-2-yl)-5-methoxybenzcarboxamide,

(31) 2-(6-(4-amidinophenylcarbamoyl)isoquinolin-7-yl)benzoic acid, methyl ester, ethyl ester, benzyl ester thereof, non-toxic salts thereof or hydroxide thereof.

- 5 11. The blood coagulation factor VIIa inhibitors which comprises a compound according to claim 1, as active ingredient.
12. Use of a compound according to claim 1 in manufacture of a medicament for the prevention and / or treatment of several angiopathy caused by enhancing a coagulation activity.
- 10 13. Use of a compound according to claim 1 in manufacture of a medicament for the prevention and / or treatment of disseminated intravascular coagulation, coronary thrombosis (e.g. acute myocardial infarction, unstable angina), cerebral infarction, cerebral embolism, transient ischemic attack, cerebrovascular disorders, pulmonary vascular diseases (e.g. pulmonary infarction, pulmonary embolism), deep venous thrombosis, peripheral arterial obstruction, thrombosis after artificial vascular transplantation and artificial valve transplantation, post-operative thrombo-
- 15 sis, reobstruction and restenosis after coronary artery bypass operation, reobstruction and restenosis after PTCA (percutaneous transluminal coronary angioplasty) or PTCR (percutaneous transluminal coronary recanalization), thrombosis by extracorporeal circulation and procoagulative diseases such as glomerulonephritis.

20

25

30

35

40

45

50

55

INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP99/00622

A. CLASSIFICATION OF SUBJECT MATTER Int.Cl ⁶ C07C257/18, A61K31/27, C07D309/04, A61K31/35, A61K31/41, C07D257/04, C07D213/78, C07D213/81, A61K31/44, C07D317/68, According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) Int.Cl ⁶ C07C257/18, A61K31/27, C07D309/04, A61K31/35, A61K31/41, C07D257/04, C07D213/78, C07D213/81, A61K31/44, C07D317/68, Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) CAPLUS (STN), CAOLD (STN), REGISTRY (STN)		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DE, 1902475, A (VEB Farbenfabrik Wolfen), 9 April, 1970 (09. 04. 70) & CH, 515968, A	1-10
A	WO, 97/23212, A1 (Du Pont Merck Pharmaceutical Company), 3 July, 1997 (03. 07. 97) & EP, 874629, A1	1-13
A	US, 5342851, A (McNeil-PPC, Inc.), 30 August, 1994 (30. 08. 94) (Family: none)	1-13
<input type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> See patent family annex.		
* Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family		
Date of the actual completion of the international search 7 May, 1999 (07. 05. 99)		Date of mailing of the international search report 18 May, 1999 (18. 05. 99)
Name and mailing address of the ISA/ Japanese Patent Office		Authorized officer
Facsimile No.		Telephone No.

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP99/00622

A. (Continuation) CLASSIFICATION OF SUBJECT MATTER

C07D307/78, C07D307/84, C07D307/22, C07D307/68, A61K31/34, A61K31/36,
C07D239/36, A61K31/505, C07D333/38, C07D333/70, A61K31/38, C07D405/12,
C07D401/10, C07D409/04, C07D211/28, A61K31/445, C07D235/08, A61K31/415

B. (Continuation) FIELDS SEARCHED

C07D307/78, C07D307/84, C07D307/22, C07D307/68, A61K31/34, A61K31/36,
C07D239/36, A61K31/505, C07D333/38, C07D333/70, A61K31/38, C07D405/12,
C07D401/10, C07D409/04, C07D211/28, A61K31/445, C07D235/08, A61K31/415